

# **Neurocognitive mechanisms of psychosis**

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# Outline

1. Reinforcement learning as an intermediate phenotype in psychosis?
2. Jumping to conclusions on basis of too little evidence as basis for delusions?
3. Learning and prediction error: belief formation, perception & psychosis



# Reinforcement learning as an intermediate phenotype in psychosis? Deficits sensitive to illness stage but not associated with polygenic risk of schizophrenia in the general population

Marcella Montagnese <sup>a</sup>, Franziska Knolle <sup>a</sup>, Joost Haarsma <sup>a</sup>, Juliet D. Griffin <sup>a</sup>, Alex Richards <sup>h</sup>, Petra E. Vertes <sup>a</sup>, Beatrix Kiddie <sup>a</sup>, Paul C. Fletcher <sup>a, b, f</sup>, Peter B. Jones <sup>a, f</sup>, Michael J. Owen <sup>h</sup>, Peter Fonagy <sup>g</sup>, Edward T. Bullmore <sup>a, c</sup>,  
<sup>f</sup>, Raymond J. Dolan <sup>d, e</sup>, NSPN Consortium, Michael Moutoussis <sup>d, e</sup>, Ian M. Goodyer <sup>a, f</sup>, Graham K. Murray <sup>a, c, f</sup>  

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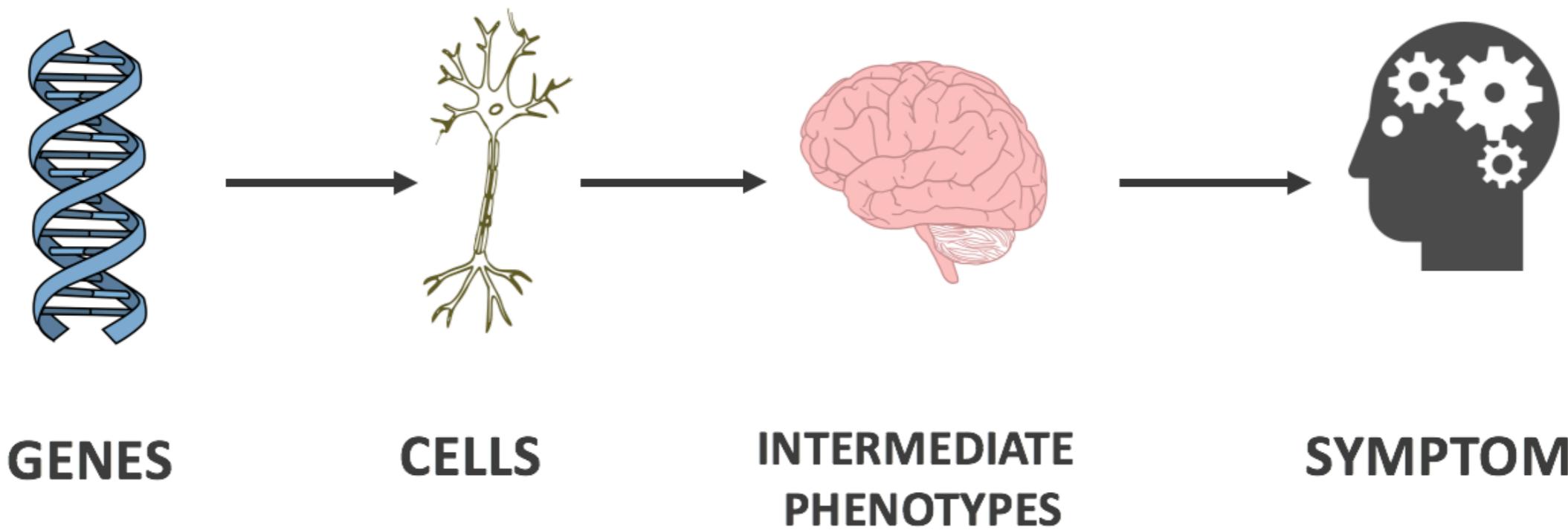
<https://doi.org/10.1016/j.schres.2020.04.022>

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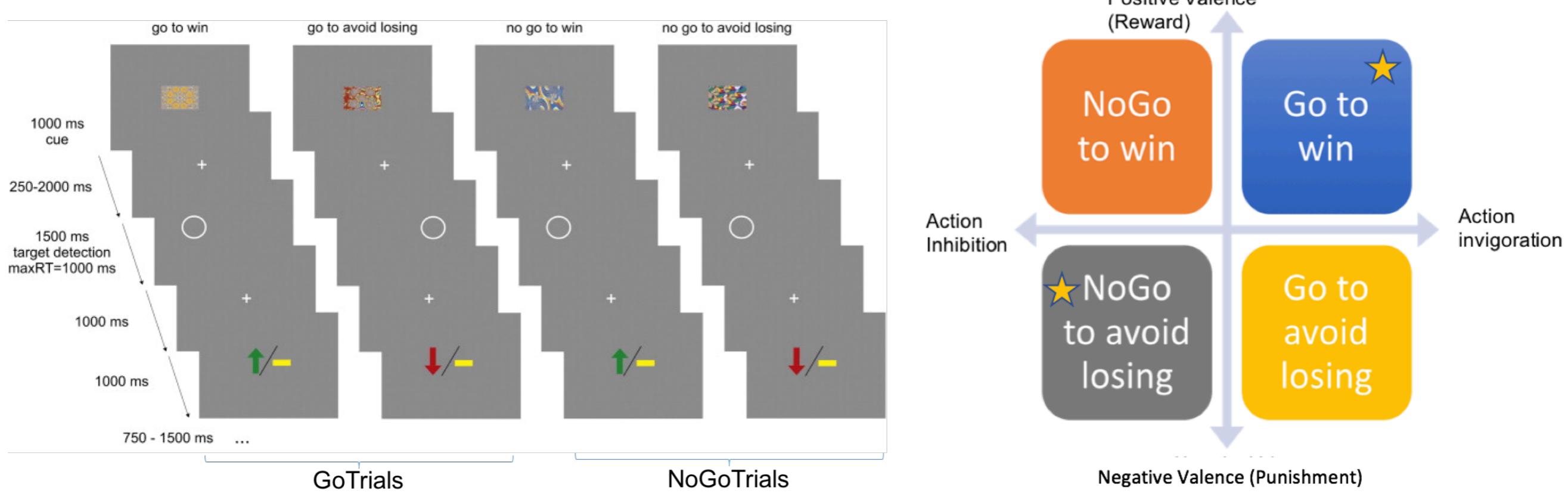
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# Intermediate Phenotype



# Go/NoGo-task paradigm (Guitart-Masip et al. 2012)



# Montagnese et al 2020

Variable	Controls (n=29)		ARMS (n=23)		FEP (n=26)		Statistics Value (df), Significance
	Mean	SD	Mean	SD	Mean	SD	
Age (years) N= 78	22.44	3.68	21.22	3.39	24.61	4.58	p<0.05 ANOVA $F(2)=4.74, p=0.011^*$
Gender (male/ female) N= 78	16/13		17/6		22/4		$\chi^2(2)=5.89, p=0.052$
IQ (Wasi) N= 70	119.72	10.35	119.59	8.18	108.44	17.50	Welch's ANOVA $F(2,45.98)=4.48, p=0.017^{**}$

# Demographics

<b>Variable</b>	<b>U-change baseline assessment (n=735)</b>	
	<b>Mean</b>	<b>SD</b>
Age (years)	18.60	2.96
Gender (male/female)	356/379	
IQ (WASI)	111.01	11.32

# Methods overview

**Unmodeled behavioural data from cognitive task (Go/No-Go task)**

**hBayesDM package (R Stan)**

**Model fitting for participants**

- ARMS, FEP and Controls as one group
- U-Change cohort as one group

**Model comparisons and predictive checks**

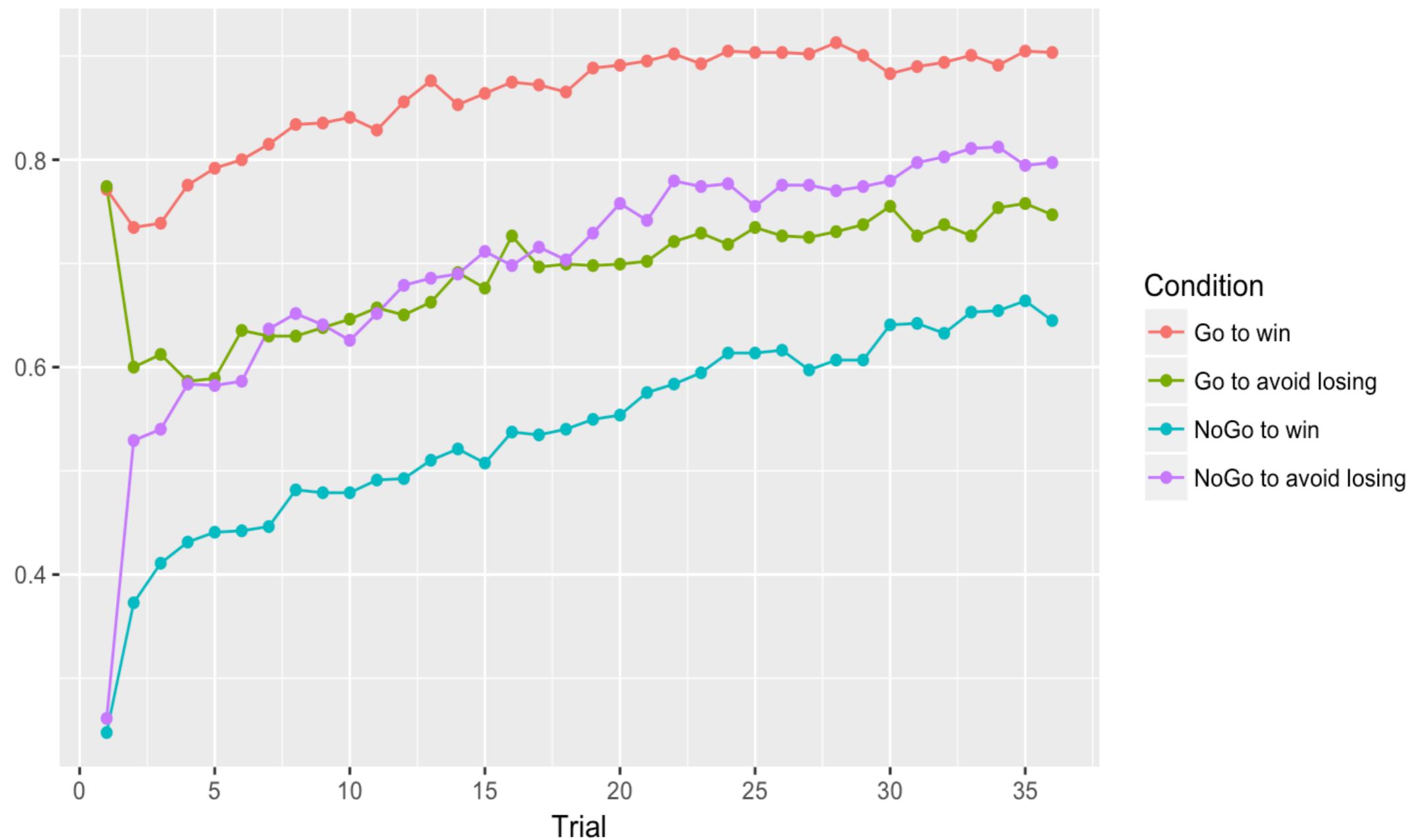
**Modelled parameters**

**Statistical analyses**

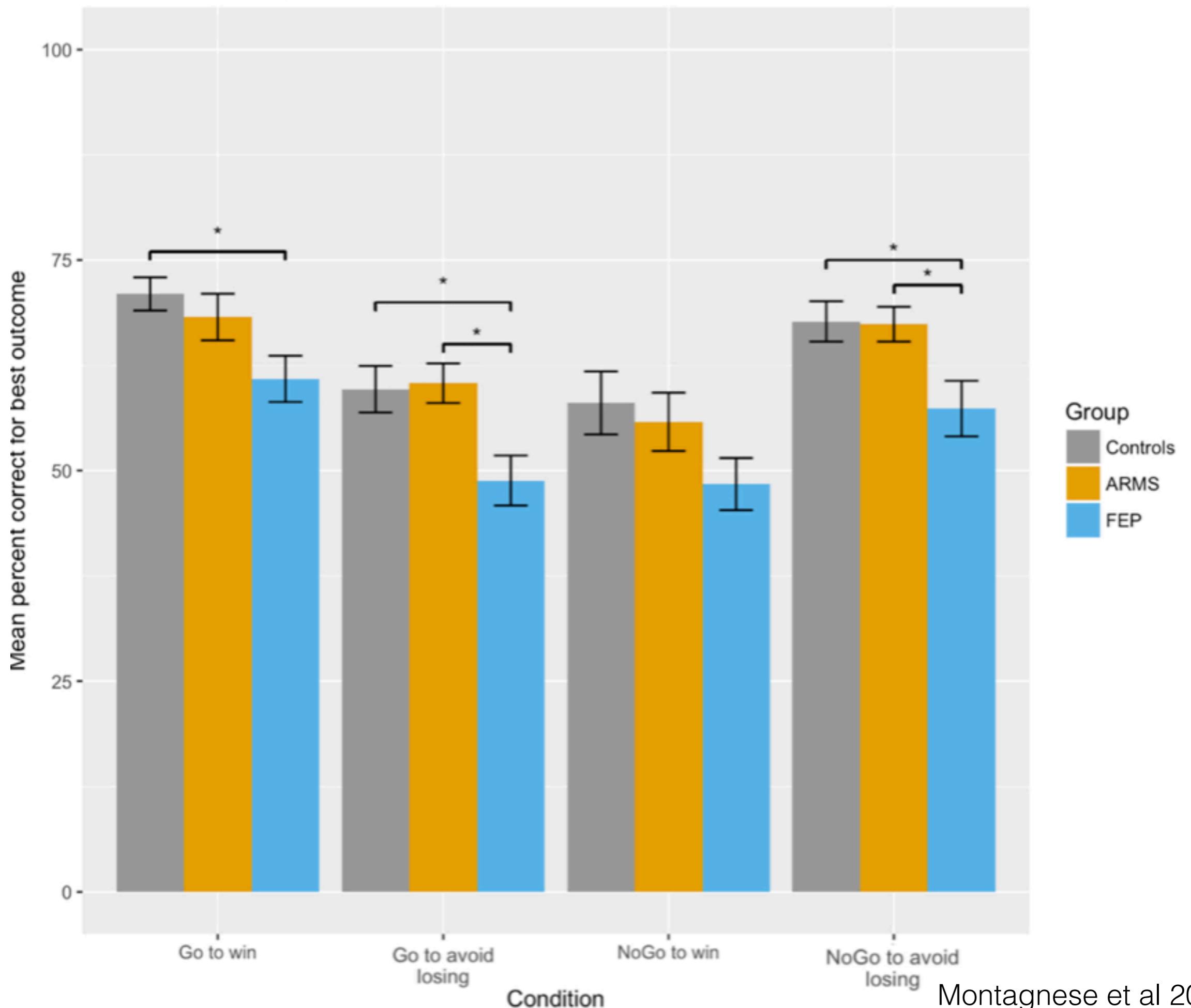


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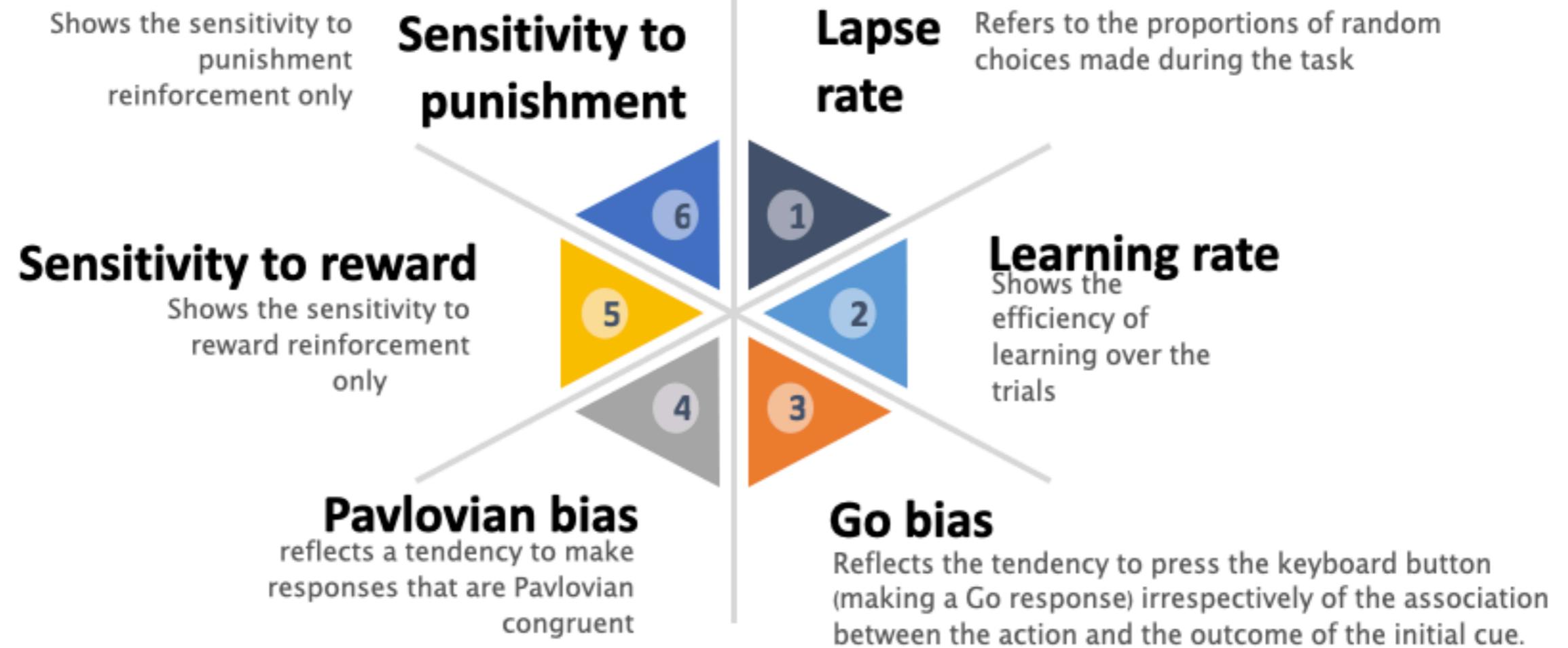
# Performance on GoNoGo RL Task, UChange (n~700)



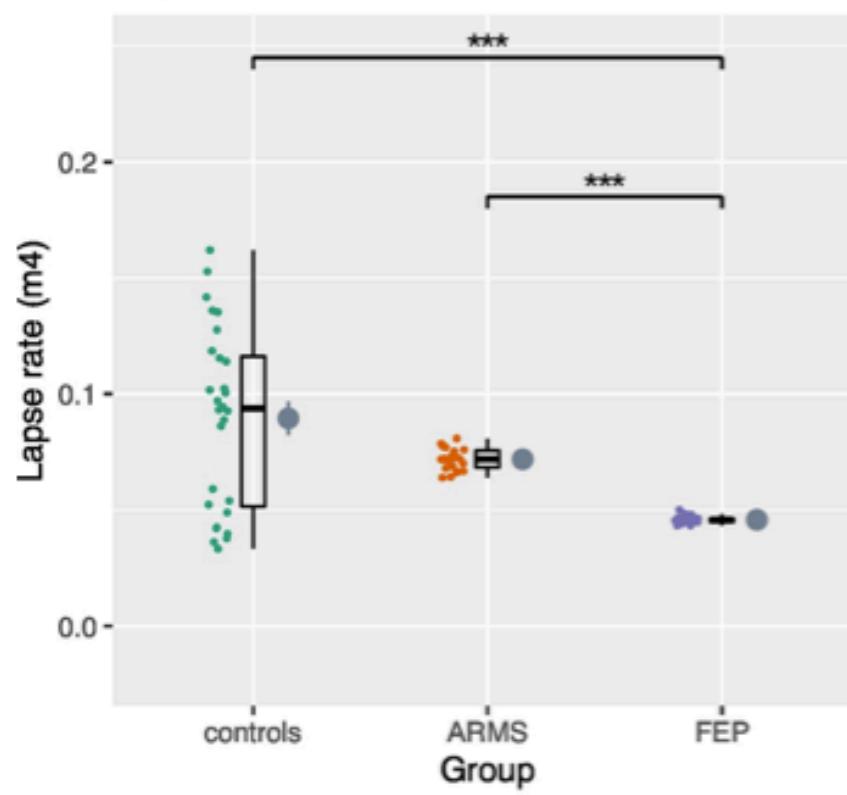
# Performance by group on the four GNG conditions (n= 75)



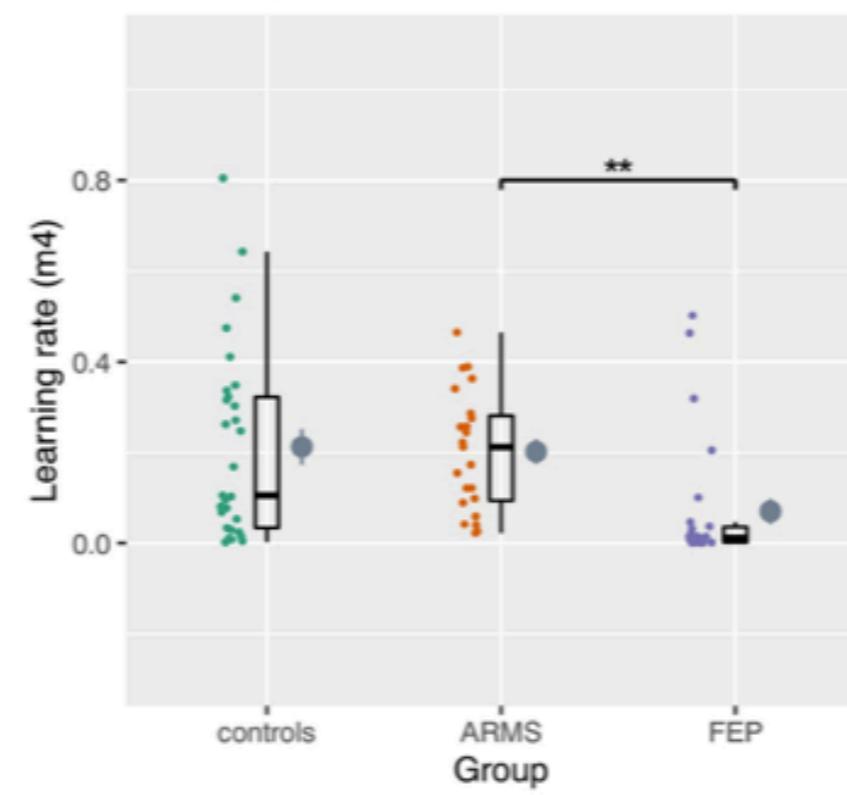
# Model 4 (Modelling in hBayesDM - thanks to developers!)



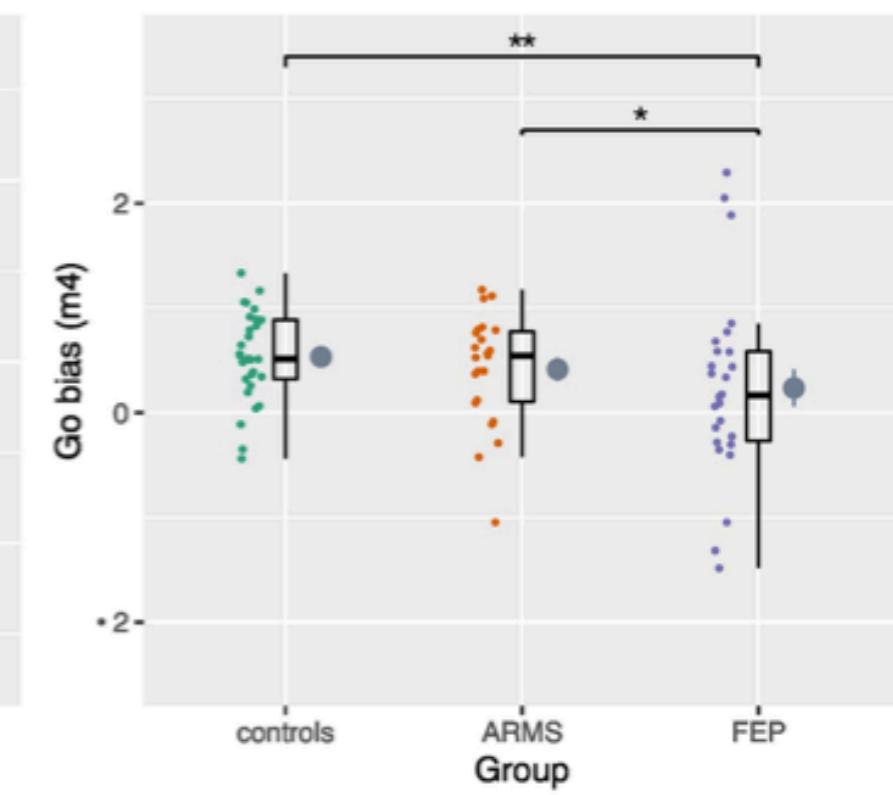
Lapse rate



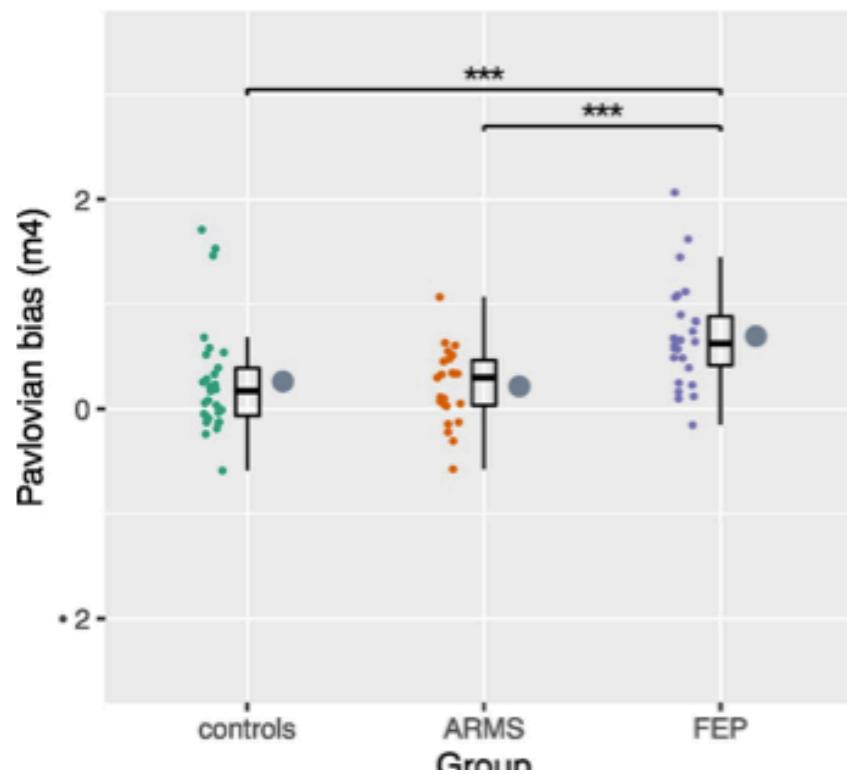
Learning rate



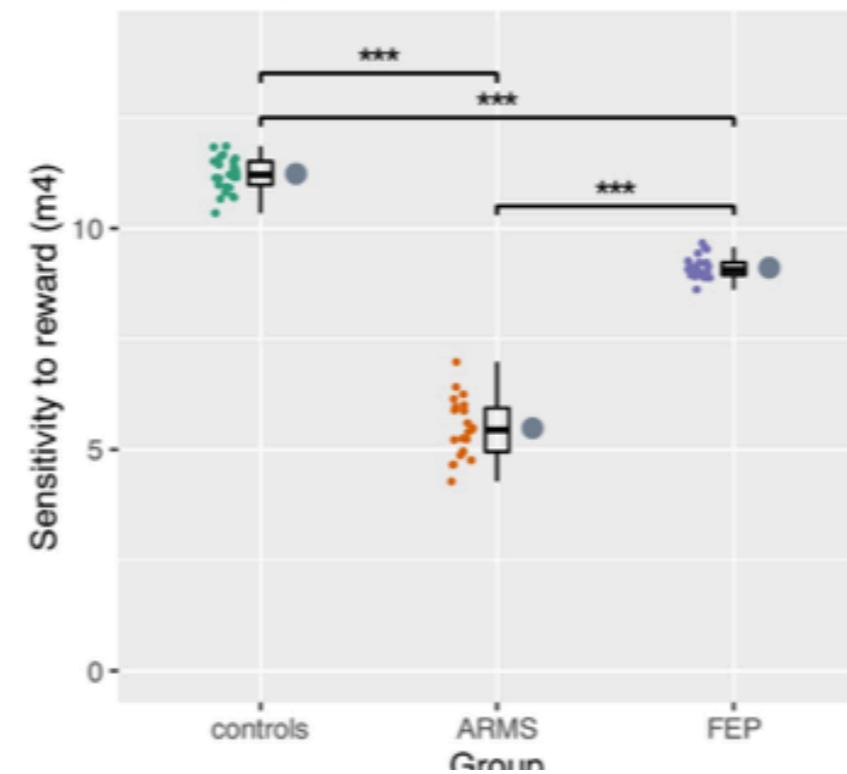
Go bias



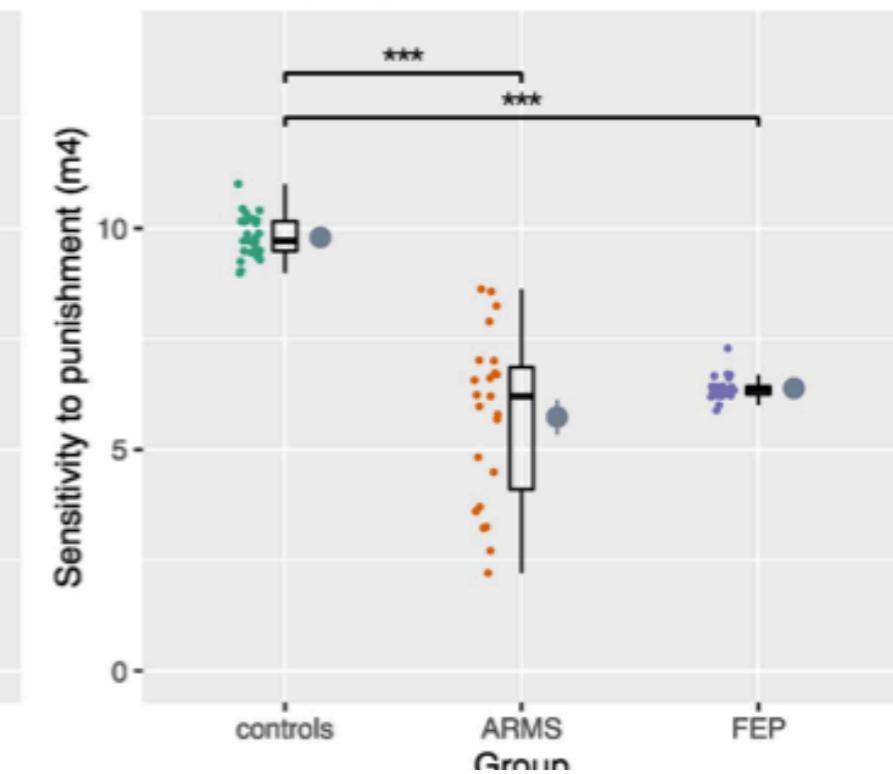
Pavlovian bias



Sensitivity to reward



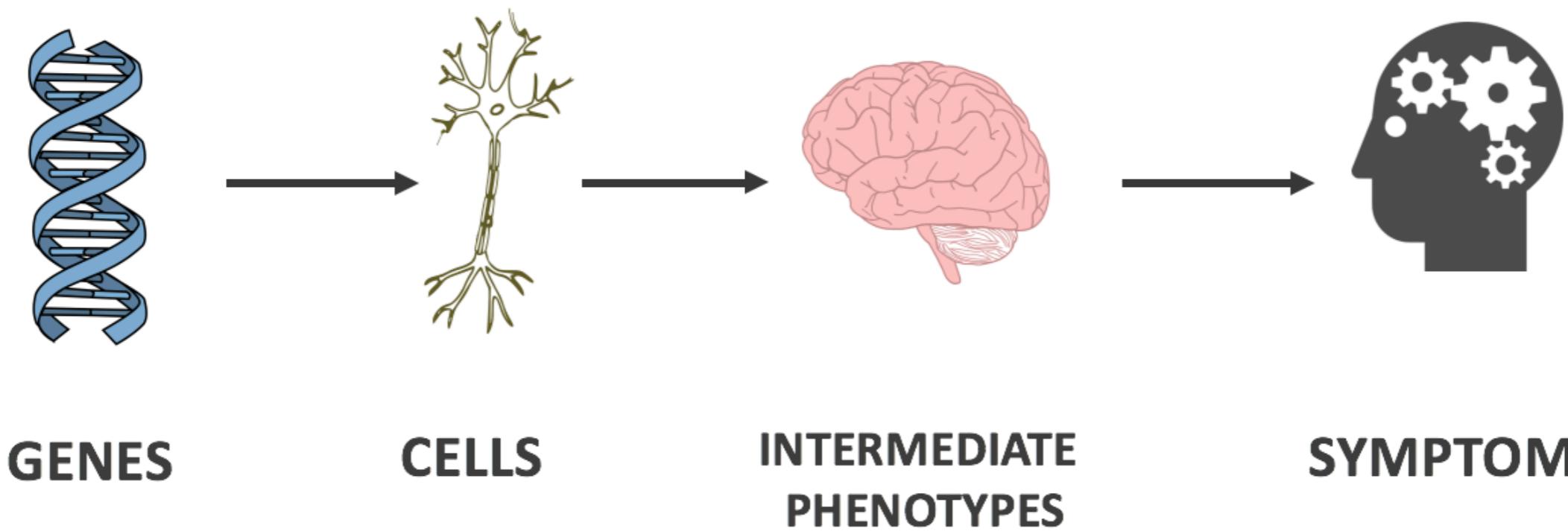
Sensitivity to punishment



**Overall, FEP impaired in all domains, both observed data and latent variables. ARMS (broadly) perform similarly to controls.**

Montagnese et al 2020

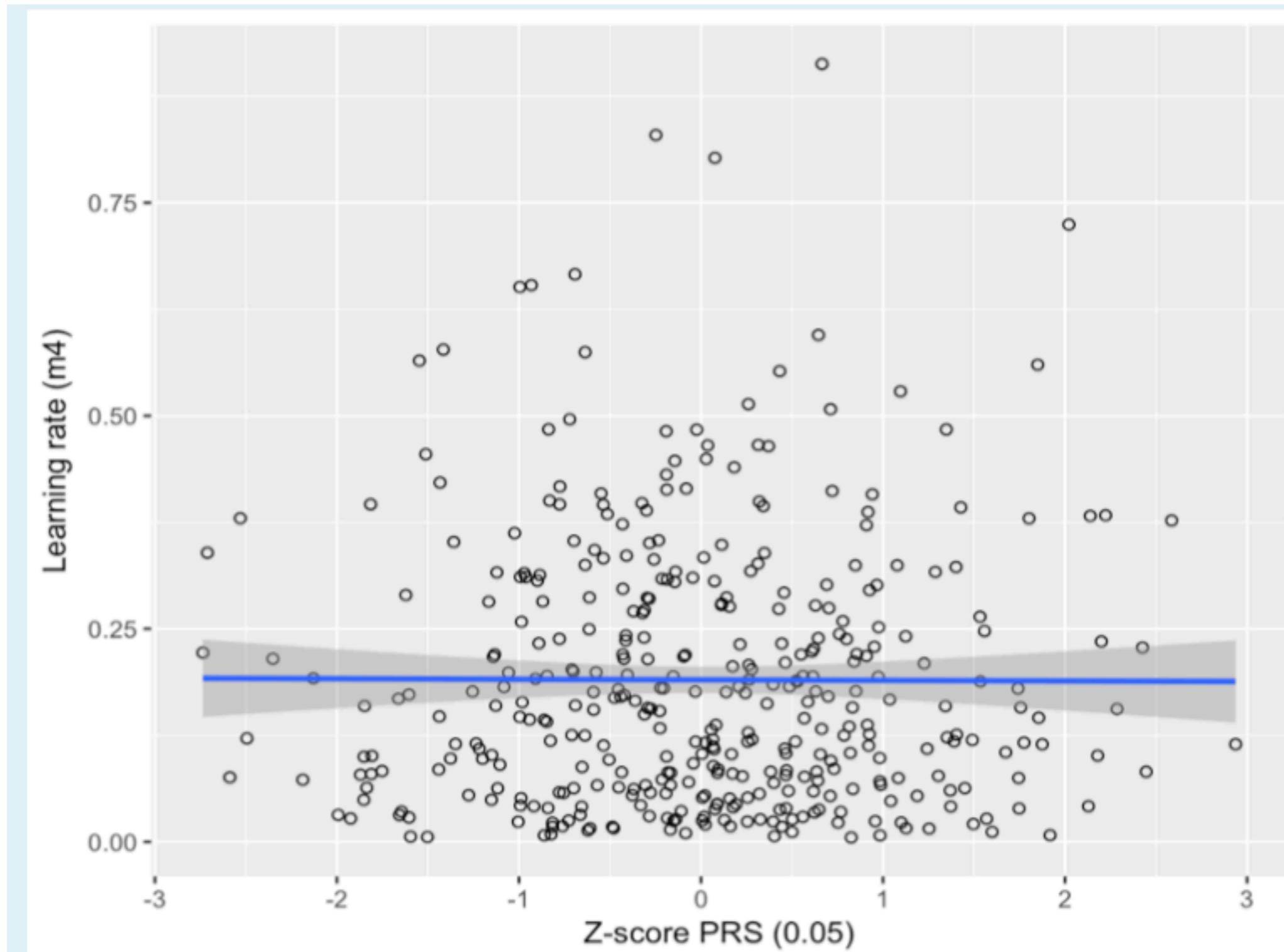
# Intermediate Phenotype



# Intermediate phenotypes and Polygenic Risk Scores

- If reinforcement learning (as measured by this task) is an intermediate phenotype for schizophrenia, it should be altered in people at the highest molecular genetic risk for schizophrenia.
- A Polygenic Risk Score (PRS) provides a summary measure of an individual's genomic propensity to a given trait, and can be used to rank individuals according to their genetic risk for the trait
  - see Wray et al for a recent 'primer' on PRS  
*JAMA Psychiatry*. 2021;78(1):101-109. doi:10.1001/jamapsychiatry.2020.3049

no association with genomic risk for schizophrenia in our data ( $n \sim 400$ )



# Summary

- FEP widely impaired, ARMS perform similarly to controls.
- No evidence for reinforcement learning (as measured this way) to be an intermediate phenotype for schizophrenia (but modest sample for genomics, other ways of measuring RL etc)
- hBayesDM was extremely useful in this project (and in other recent works, such as Suetani et al MedRxiv 2021)

[Comment on this paper](#)

**Impairments in goal-directed action and reversal learning in a proportion of individuals with psychosis: evidence for differential phenotypes in early and persistent psychosis**

• Shuichi Suetani, Andrea Baker, Kelly Garner, Peter Cosgrove, Matilda Mackay-Sim, Dan Siskind, Graham K Murray, James G Scott, James P Kesby

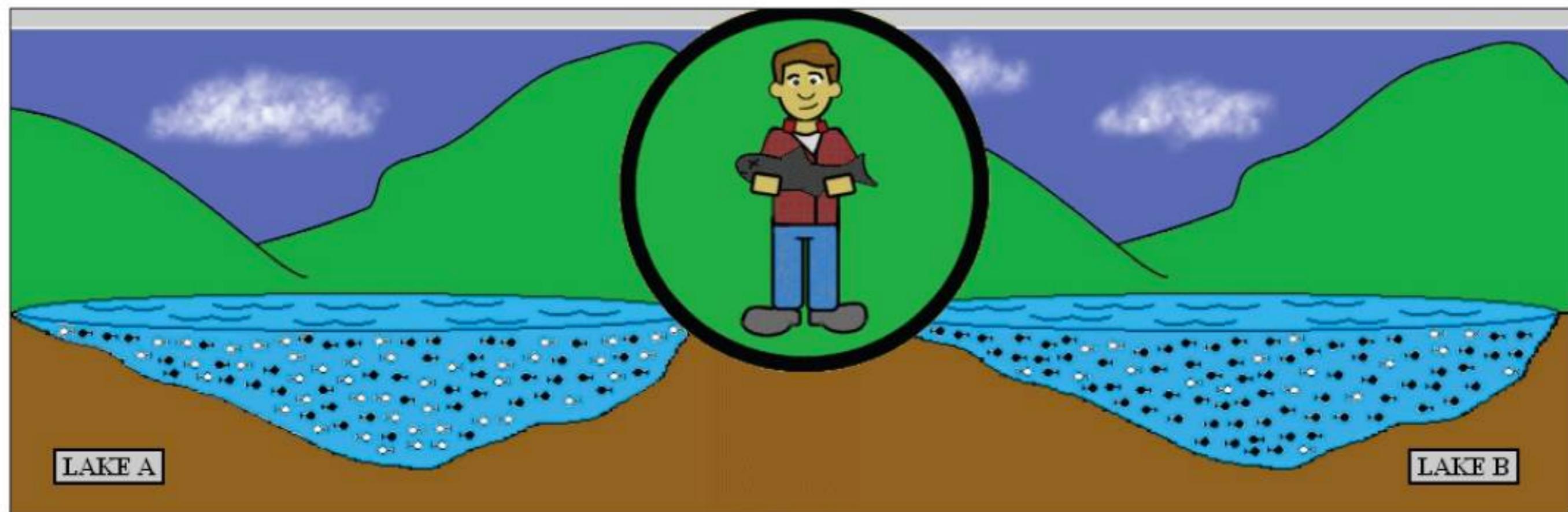
• doi: <https://doi.org/10.1101/2021.08.31.21262937>

# Outline

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2. Jumping to conclusions on basis of too little evidence as basis for delusions?
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# “Jumping to conclusions”

- Patients with schizophrenia, especially with delusions, sample less information than controls before reaching a decision - confirmed on meta-analysis, Fine et al 2007



Ratio 60:40

Speechley et al 2010

Ratio 40:60

# Cost of sampling information

- Why do patients sample less information? Are they "noisy" decision makers, with more randomness in decisions? Or do they attribute a greater cost to sampling information?
- Moutoussis and colleagues (2011) studied this in chronic schizophrenia, and found a greater “noise” in decision making, rather than greater perceived sampling costs, best accounted for group differences.
- They concluded that the Jumping-to-Conclusions Bias is unlikely to be due to an overestimation of the cost of gathering more information.

COGNITIVE NEUROPSYCHIATRY  
2011, 16 (5), 422–447

 Psychology Press  
Taylor & Francis Group

**Bayesian modelling of Jumping-to-Conclusions  
bias in delusional patients**

Michael Moutoussis<sup>1</sup>, Richard P. Bentall<sup>2</sup>,  
Wael El-Deredy<sup>1</sup>, and Peter Dayan<sup>3</sup>

# Our aim

- Need to study early stages of psychosis, in sample with relatively preserved general cognitive function. We used an early psychosis sample (patient n=31, control n=31), patient mean IQ > 100. Mainly unmedicated.
- Modify classical experiment to have some blocks without explicit cost of sampling information but also some blocks where there is a cost to sampling new information



Continuous Publication  
Founded: 2017  
E-ISSN: 2379-6227

## **Cost Evaluation During Decision-Making in Patients at Early Stages of Psychosis**

[Anna O. Ermakova](#), [Nimrod Gileadi](#), [Franziska Knolle](#) ,  
[Azucena Justicia](#), [Rachel Anderson](#), [Paul C. Fletcher](#),  
[Michael Moutoussis](#)  and [Graham K. Murray](#) 

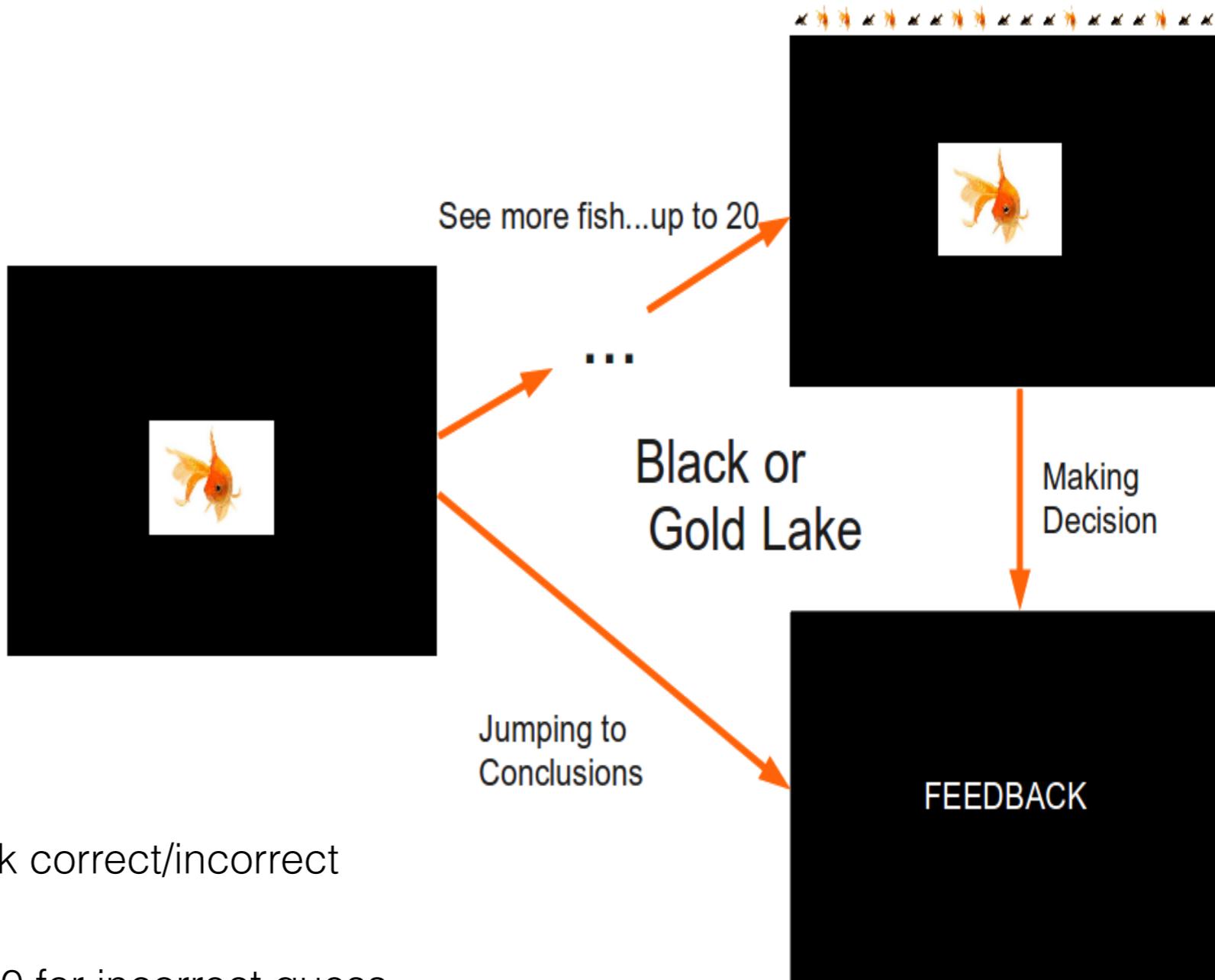
Posted Online February 01, 2019  
[https://doi.org/10.1162/cpsy\\_a\\_00020](https://doi.org/10.1162/cpsy_a_00020)

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**Computational Psychiatry**  
Volume 3, 2019  
p.18-39

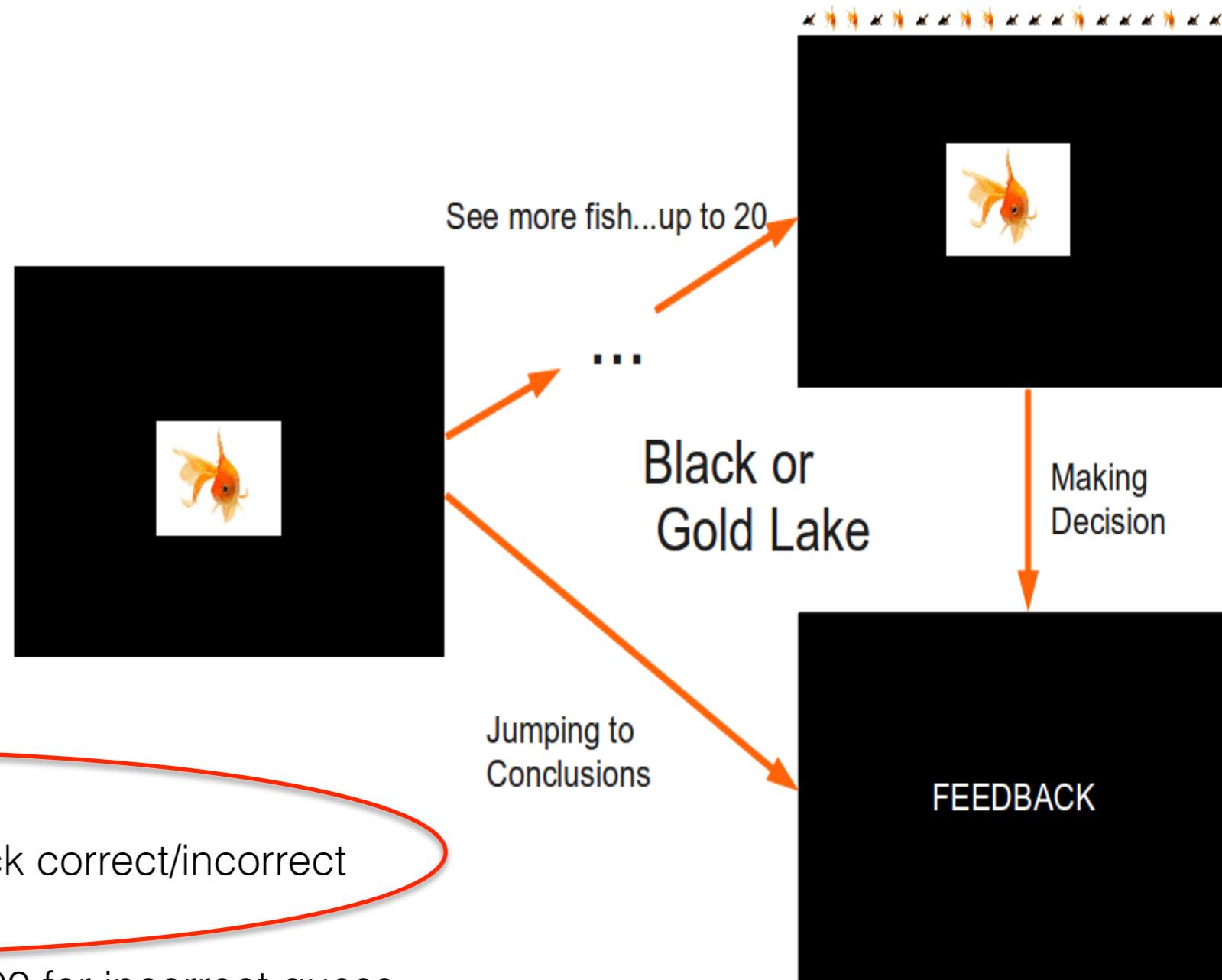
# JTC Task

- Fishes task over 4 blocks
  - Draws to Decision analysed
- 1) Block 1: No sampling cost, feedback correct/incorrect
  - 2) Block 2: +100 for correct guess, -100 for incorrect guess
  - 3) Block 3: Same reward/loss values, but -5 points for each extra sample
  - 4) Block 4: Same reward/loss values, but incremental increase in cost of samples (0, -5, -10)



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# Computational “Costed Bayesian” model

- An ideal Bayesian agent chooses the option that maximizes its expected reward.
- Parameters –
  - Cost of Sampling parameter: higher values mean earlier decisions
  - Noise Parameter: as value increases, behaviour more random
  - Random effects model using expectation maximisation to fit the group mean and variance for each parameter.
- Use BIC to determine whether behaviour best explained by patients and controls coming from one distribution with a single mean & variance of each parameter, or coming from two separate distributions.

The agent is faced with a choice of three actions:

- Declare lake black(DB)
- Declare lake gold(DG)
- Ask for another fish-“sample again”(DS)

$$Q(D_G; n_d, n_g) = R_C P(G|n_d, n_g) - C_W P(B|n_d, n_g)$$

Where:

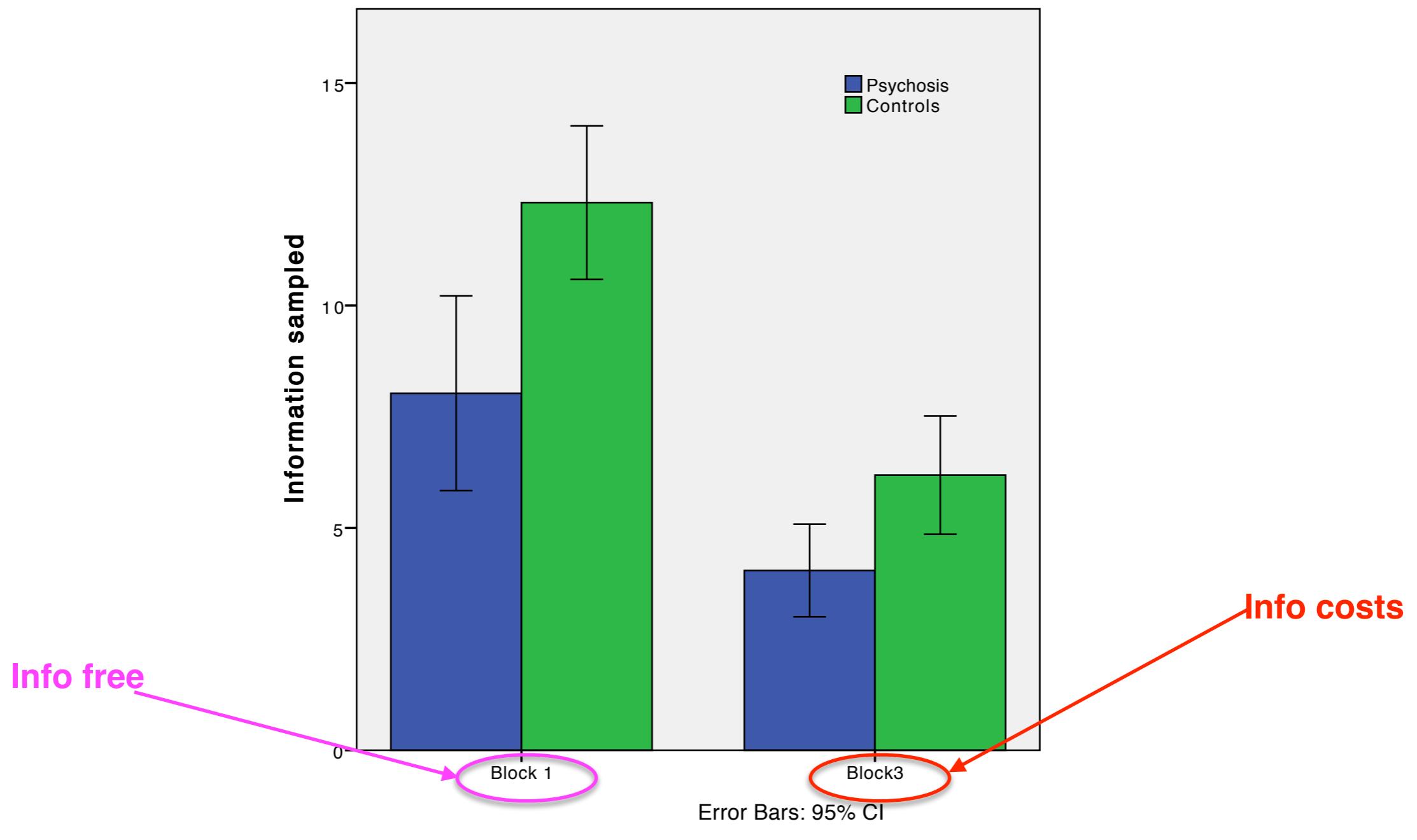
$Q(D_G; n_d, n_g)$  is the action value of declaring the lake black, after drawing  $n_d$  fish and seeing  $n_g$  gold fish.

$P(G|n_d, n_g)$  is the probability of the lake being gold, after drawing  $n_d$  fish and seeing  $n_g$  gold fish.

$R_C$  is the reward for correctly declaring the colour of the lake.

$C_W$  is the cost of incorrectly declaring the colour of the lake.

# Psychosis patients jump to conclusions, especially when information is cheap

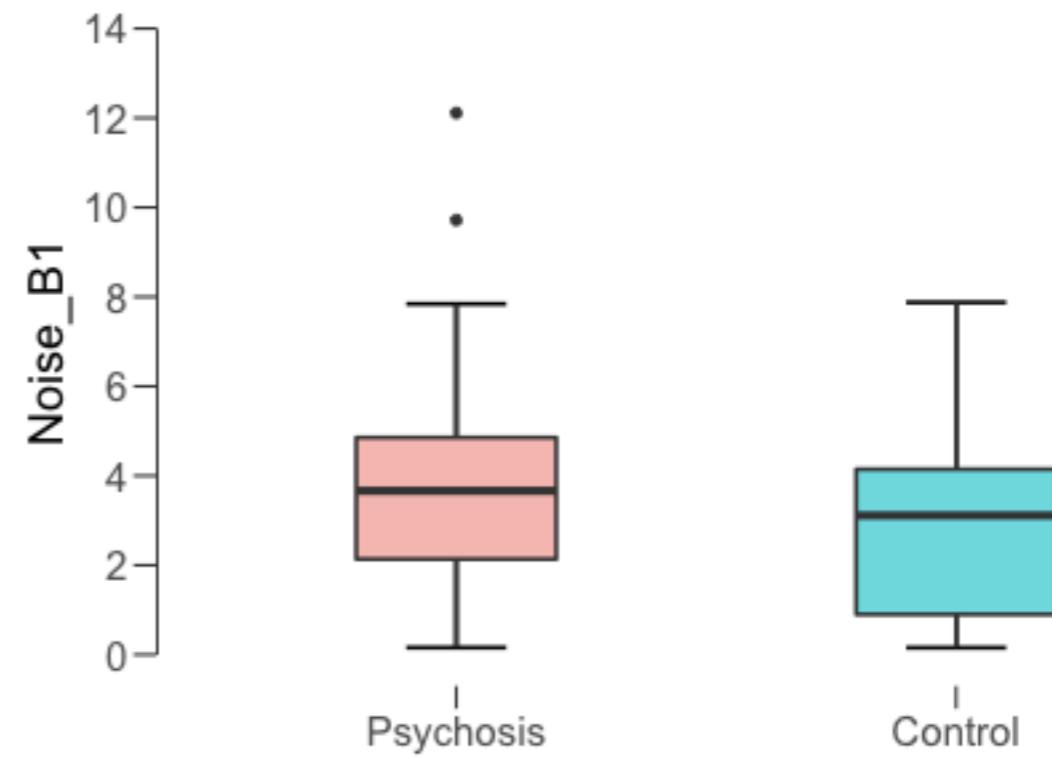
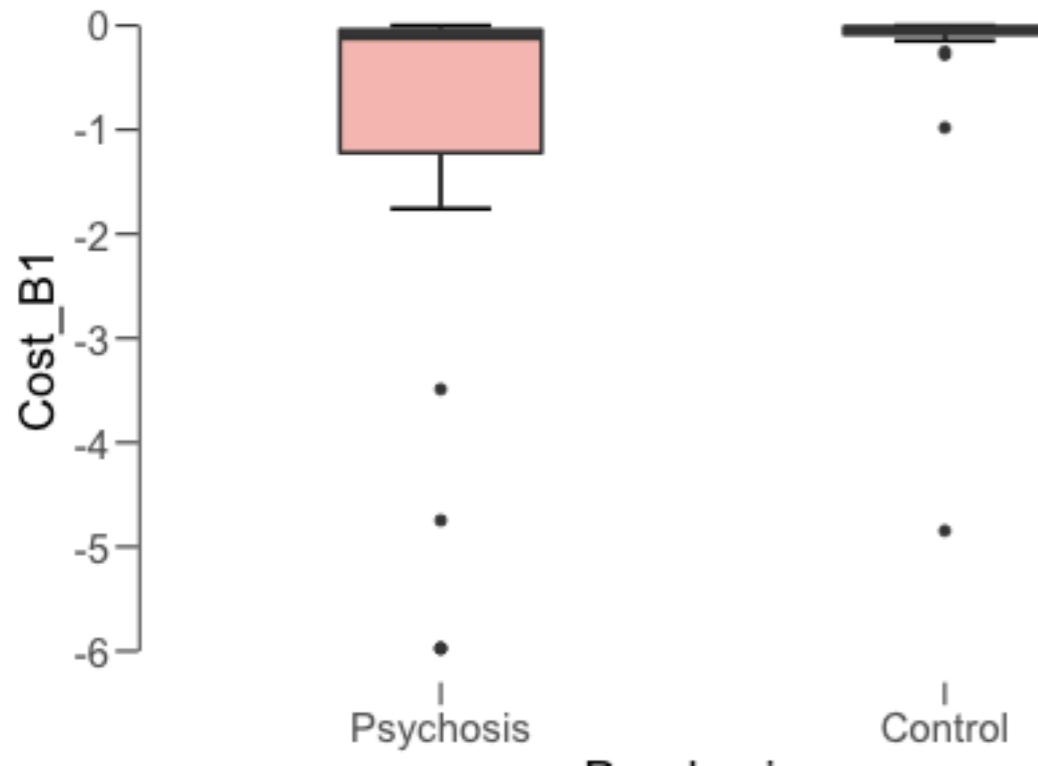


Block	iBIC combined	iBIC separate	iBIC Difference
1 (no cost)	3489.7	3450.2	39.5 (Very strong)
3 (fixed cost, plus win or loss $\pm 100$ )	2539.3	2543.4	-4.1 (Preference for combined model)

BIC values for model where all participants are drawn from the same distribution, vs model where healthy and psychosis groups differ in their distributions.

In the first two blocks, there is strong evidence that psychosis participants behave differently from the control group.

In block 3, BIC suggests no difference between the two groups: Confirmation that introducing the experimental manipulation of a cost makes the groups more similar in behaviour.  
Results similar after excluding medicated patients and low IQ patients



Modelling supported group differences in ***cost parameter*** with similar amounts of noise per group, including after matching closely on IQ.

Cost: Case v Controls p=0.007 (Block 1); p=0.04 (Block 3)

Noise: Case v Controls p=0.07 (Block 1); p=0.2 (Block 3)

Ermakova et al 2019

# The Ideal Bayesian Agent – Cost of Sampling

- In trials with no cost to additional draws (Blocks 1 & 2) patients weight cost of sampling more highly
  - Controls = 0.0019
  - Patients = 1.7
- In trials where the cost of sampling is 5 (Block 3) patients only slightly overestimate
  - Controls = 1.6 (underestimate)
  - Patients = 5.2 (very close)

# Information Sampling Summary

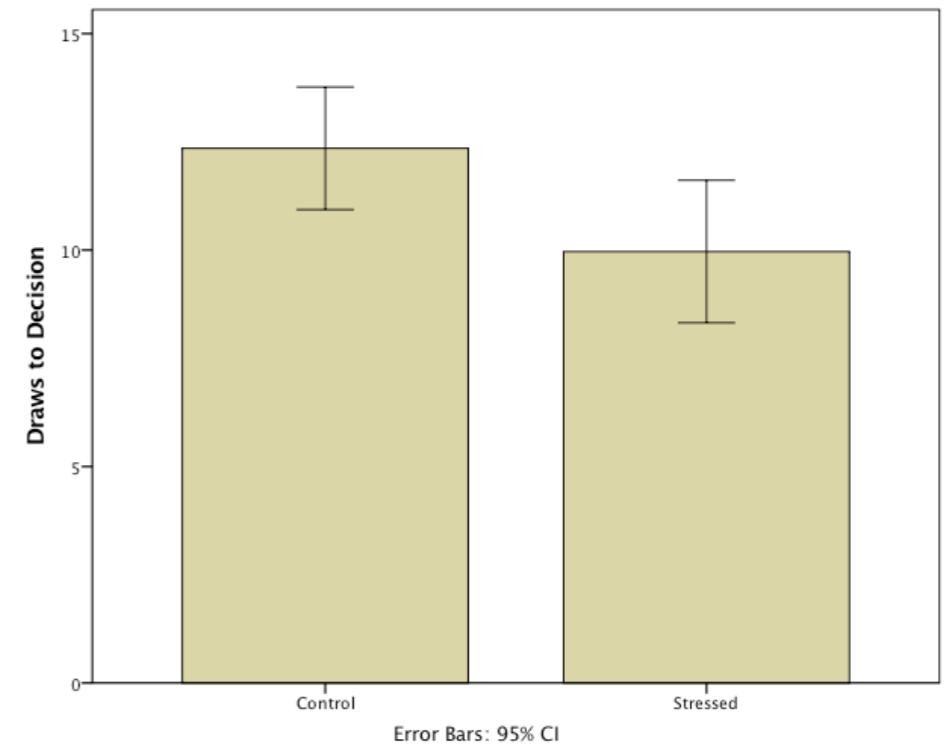
- Evidence from experimental psychology and computational modelling that patients with early psychosis jump to conclusions due to attributing excessive cost to gathering information.
- A jumping to conclusions style of reasoning is unhelpful in some circumstances but adaptive in others.
- Later in the course of schizophrenia (perhaps as in Moutoussis et al 2011) the bias may be accounted for not by the cost of information sampling but by more random decision making.

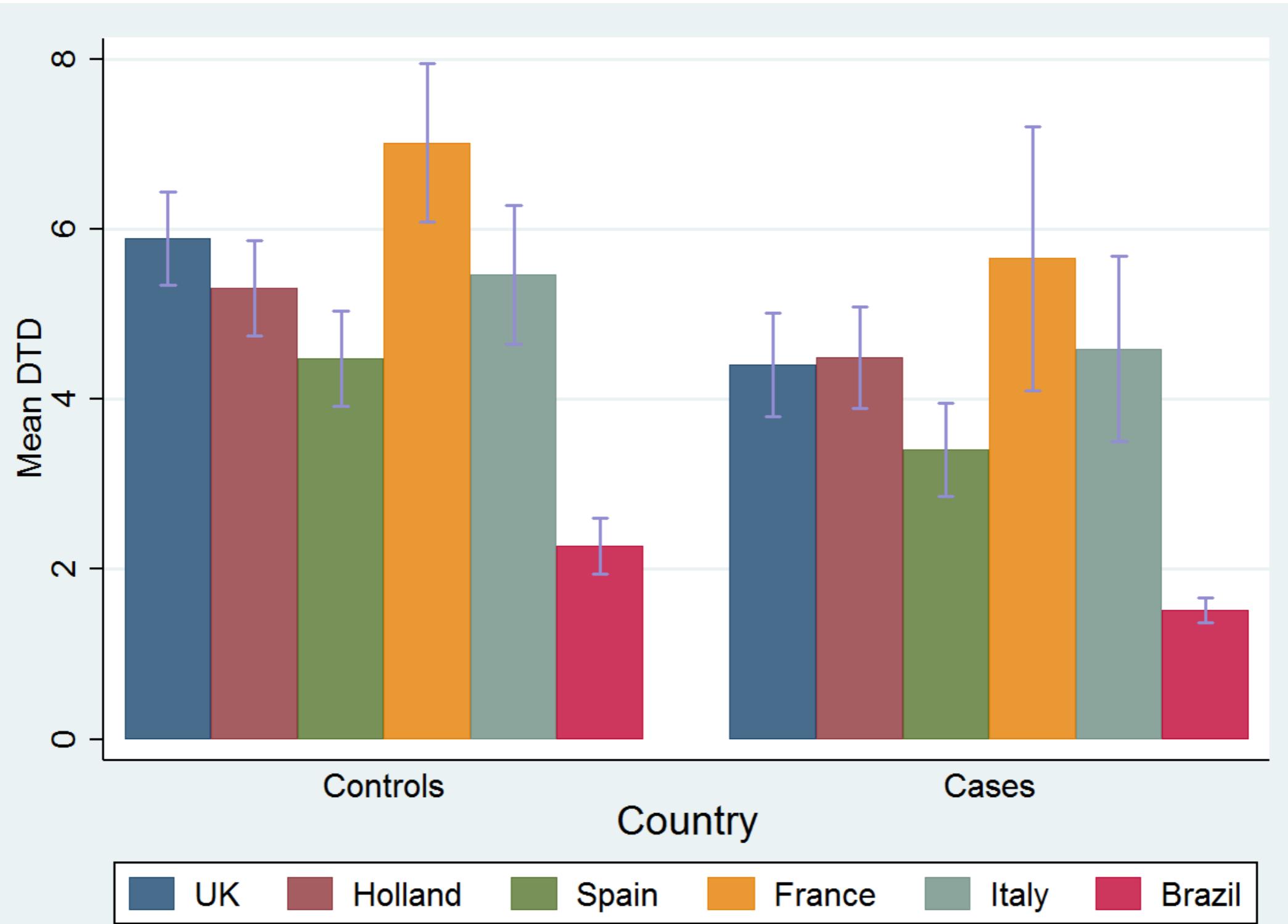
# Relation to symptoms & IQ

- Individually estimated greater cost parameters predicted more psychotic symptom severity in patients ( $\rho=0.58$ ,  $p=0.001$ ).
- There was no significant association between estimated noise parameters and psychotic symptom severity ( $\rho=0.27$ ,  $p=0.14$ ).
- Cost and noise parameters were related to each other (e.g., on Block 1,  $\rho = 0.7$ )
- IQ vs. Block 1 cost,  $\rho = 0.3$ ; Block 3,  $\rho = 0.3$ ; Block 1 noise,  $\rho = 0.2$ ; Block 3 noise,  $\rho = 0$

# What influences information sampling?

- Cognitive framing. Yes
- Stress induction: Yes.
- Drugs?
  - Amphetamine - No. Ermakova et al 2014
  - L-Dopa - No. Andreou et al 2013
  - Ketamine - No. Evans et al 2012
  - Ropinirole - Yes. Vicario-Feliciano et al 2019
    - note used costed version of task
- Genetics? Risk for schizophrenia? IQ?  
Culture?





Giada Tripoli et al 2020 (Psychological Medicine) in  
EU-GEI study.

1294 Controls v 817 Psychosis patients ( $p < 10^{-8}$ )

# Genetic risk score for IQ, but not for schizophrenia, predicts information sampling

	B/SE	P value	95% CI	R <sup>2</sup>
Case vs Control <sup>a</sup>	-0.88/0.25	0.001	-1.38 to -0.38	0.09
SZ PRS <sup>a</sup>	0.16/0.34	0.64	-0.51 to 0.82	0.09
SZ PRS <sup>b</sup>	0.47/0.35	0.17	-0.21 to 1.16	0.09
IQ PRS <sup>a</sup>	0.50/0.13	<0.001	0.25 to 0.75	0.1
IQ PRS <sup>b</sup>	0.47/0.13	<0.001	0.22 to 0.72	0.1

<sup>a</sup>Adjusted for age, gender, and 20 principal components for population stratification

<sup>b</sup>Adjusted for case/control, age, gender, and 20 pcs for population stratification

Giada Tripoli et al 2020 EU-GEI study. (1,041 controls and 679 cases)

# Relation to Symptoms

## EU-GEI

- In controls: CAPE positive symptoms negatively associated with the number of beads requested (even after controlling for age, sex, ethnicity, IQ and country ( $B = -1.7$ , 95% CI  $-2.8$  to  $-0.5$ ,  $p = 0.006$ )).
- No clear associations with symptoms in patients.

# Summary

- IQ plays a key role in information sampling (though does not preclude this being important for mechanisms of psychosis).
- Links with symptoms more robust in controls than patients.
- In classic “uncosted” version of the task, with only 1 trial, can’t distinguish between noise and “cost” bias
- Now looking at genetic and other predictors in costed version of task with 40 trials (n=700 UChange) ...
- Active research on drug/cognitive interventions to alter information sampling
- This cognitive process can be assessed in experimental animal models

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# Associative and reinforcement learning

- We learn through experience what features of the environment are connected and important
- Dysfunctional learning could lead to forming abnormal associations between unconnected phenomena, and to irrelevant stimuli acquiring inappropriate significance (cf aberrant salience)
- Prediction error (surprise) = mismatch between expectation and outcome
- Prediction error key to learning

# Importance of prediction

- Prediction error important for belief update, hence relevant for delusions
- Are theories of disrupted learning and prediction in psychosis also relevant for hallucinations?
- Prediction errors are salient, and signal attention should be allocated.

Knolle et al. *Translational Psychiatry* (2018)8:196  
DOI 10.1038/s41398-018-0250-3

Translational Psychiatry

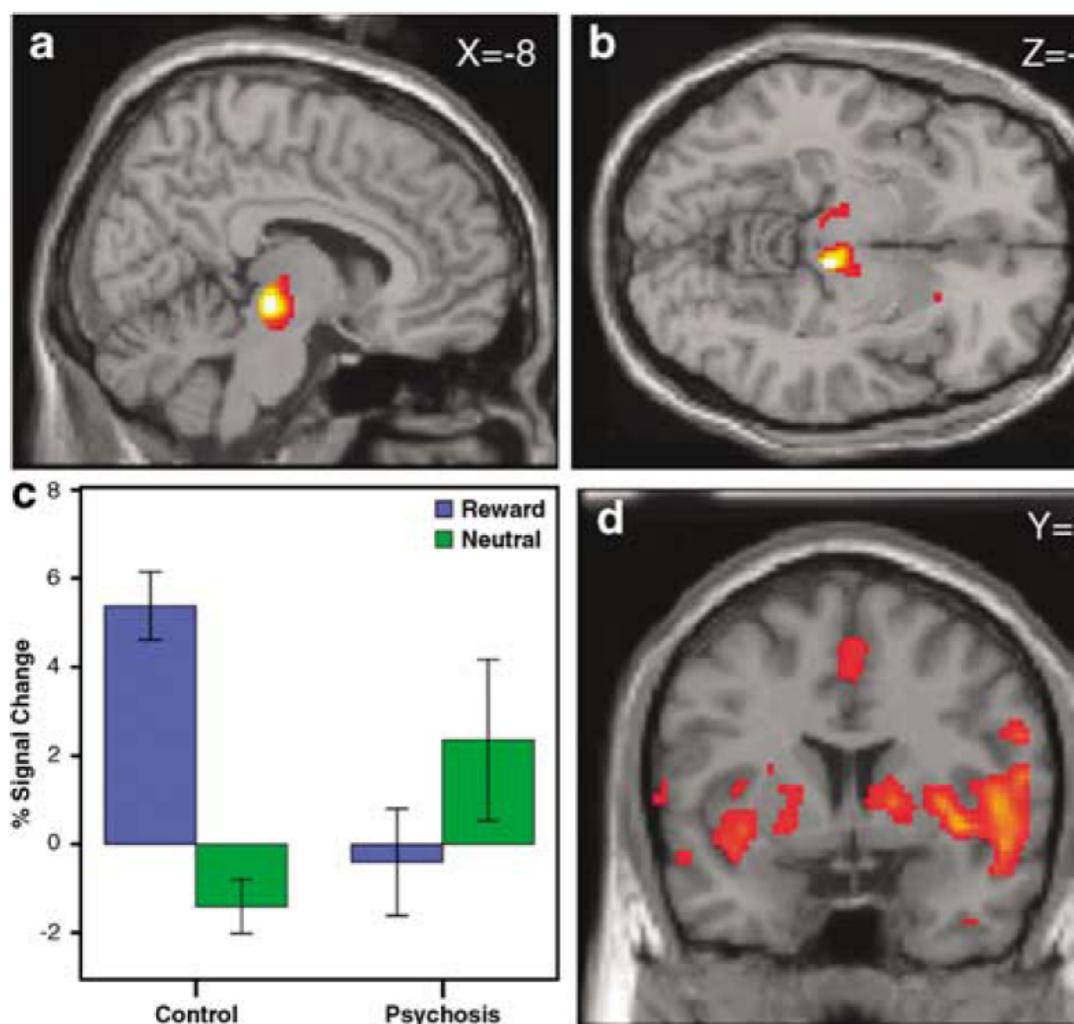
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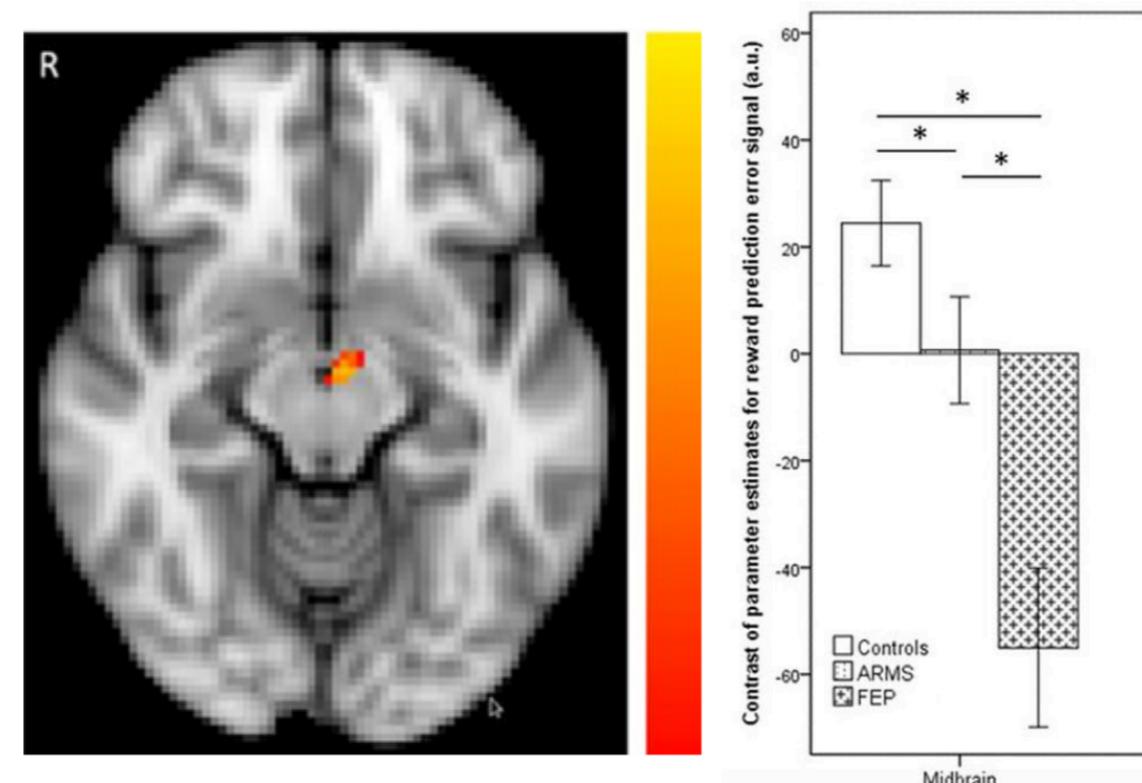
**Brain responses to different types of salience in antipsychotic naïve first episode psychosis: An fMRI study**

Franziska Knolle<sup>1,2</sup>, Anna O Ermakova<sup>3</sup>, Azucena Justicia<sup>3,4</sup>, Paul C Fletcher<sup>3,5,6</sup>, Nico Bunzeck<sup>6,7</sup>, Emrah Düzell<sup>8,9</sup> and Graham K Murray<sup>2,3,5</sup>

# Brain Prediction Error Signals Abnormal in Psychosis



Murray, Corlett et al 2008,



Neuropsychopharmacology

[www.nature.com/npp](http://www.nature.com/npp)



ARTICLE    OPEN

Abnormal reward prediction-error signalling in antipsychotic naive individuals with first-episode psychosis or clinical risk for psychosis

Anna O. Ermakova <sup>1,2</sup>, Franziska Knolle <sup>1,2</sup>, Azucena Justicia<sup>1,3</sup>, Edward T. Bullmore <sup>1,2,3</sup>, Peter B. Jones <sup>1,2,3</sup>, Trevor W. Robbins<sup>2,4</sup>, Paul C. Fletcher<sup>1,2,3,5</sup> and Graham K. Murray<sup>1,2,3</sup>

Neuropsychopharmacology (2018)

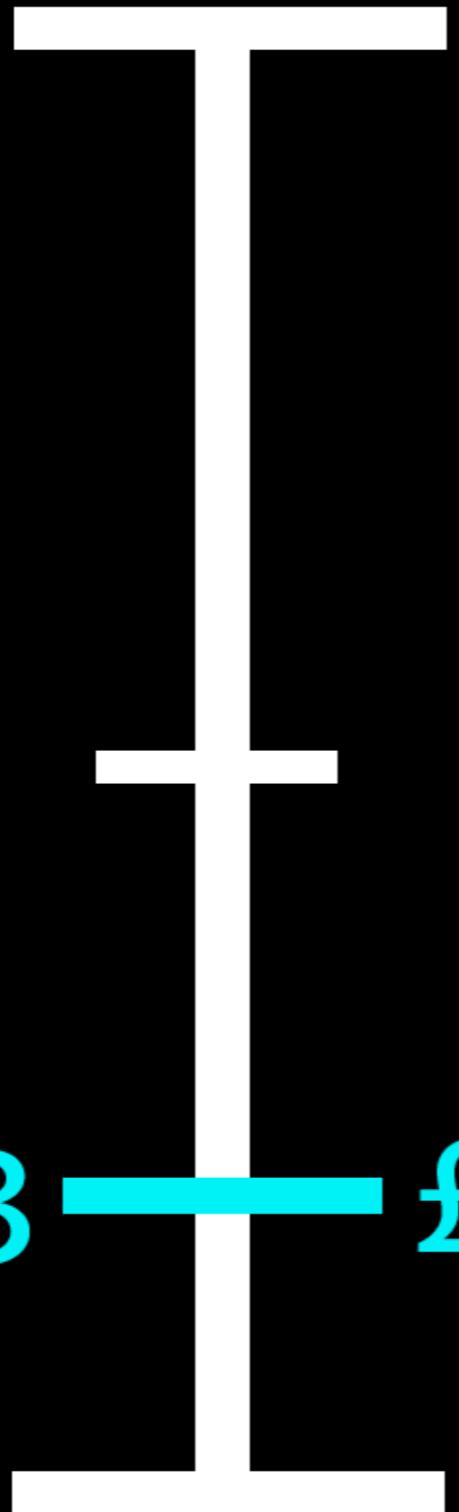
# Learning under uncertainty - role of precision

- When there is uncertainty in the environment, optimal learning should take this into account when learning and updating beliefs
- This can be formalised as updating beliefs by prediction errors scaled by a metric of uncertainty - termed precision (or inverse variance)
- Could failing to adapt learning to the environmental uncertainty (precision) contribute to psychotic symptom pathogenesis?

# Hypothesis

- Psychosis is associated with a failure to take into account the precision when updating the brain's model of the world
  - Impaired, or absent, precision-weighted model-updating brain signals in psychosis.
- To test this, use a task where we can see brain prediction error signals at varying levels of precision

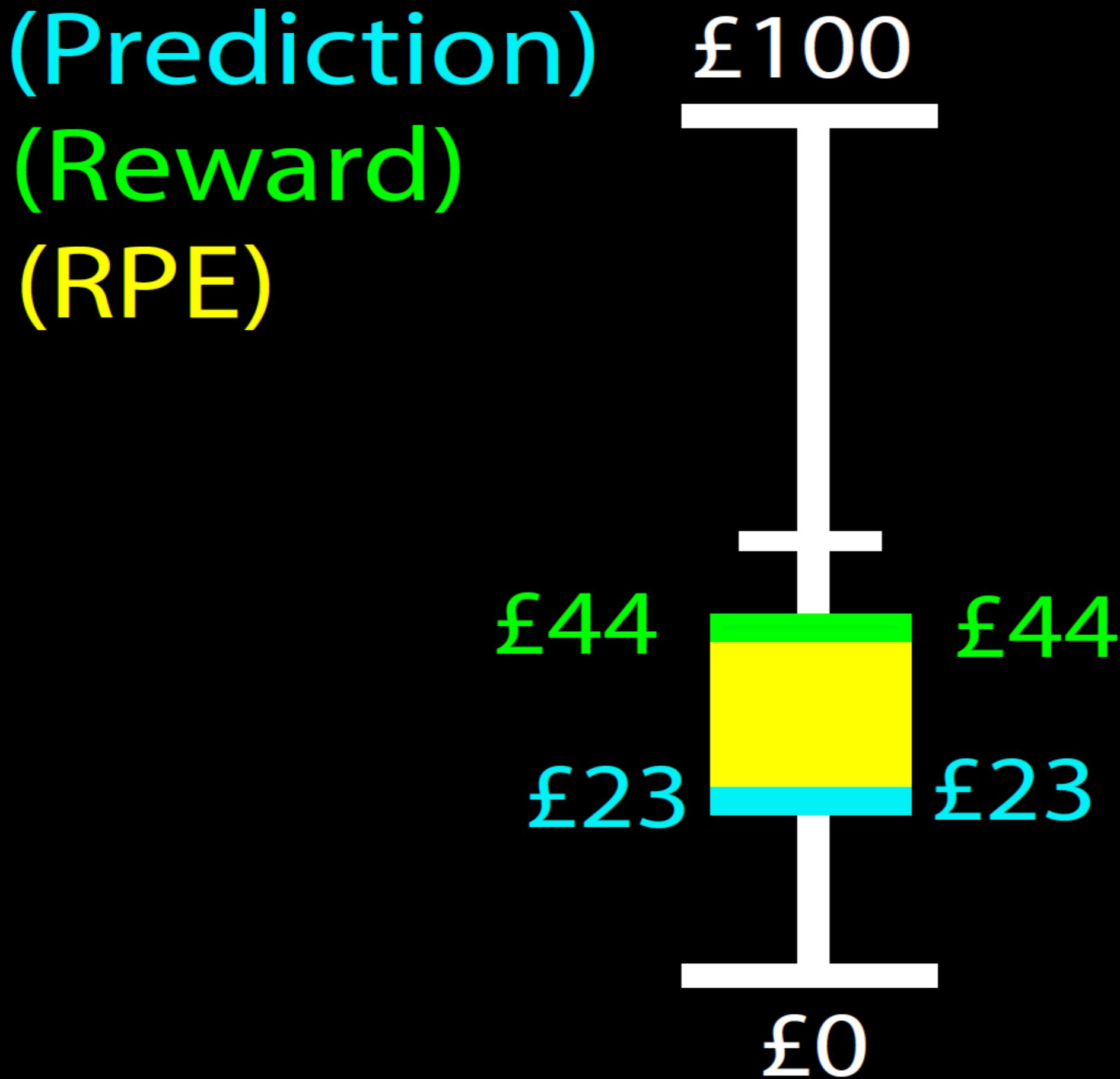
(Prediction) £100



£23 — £23

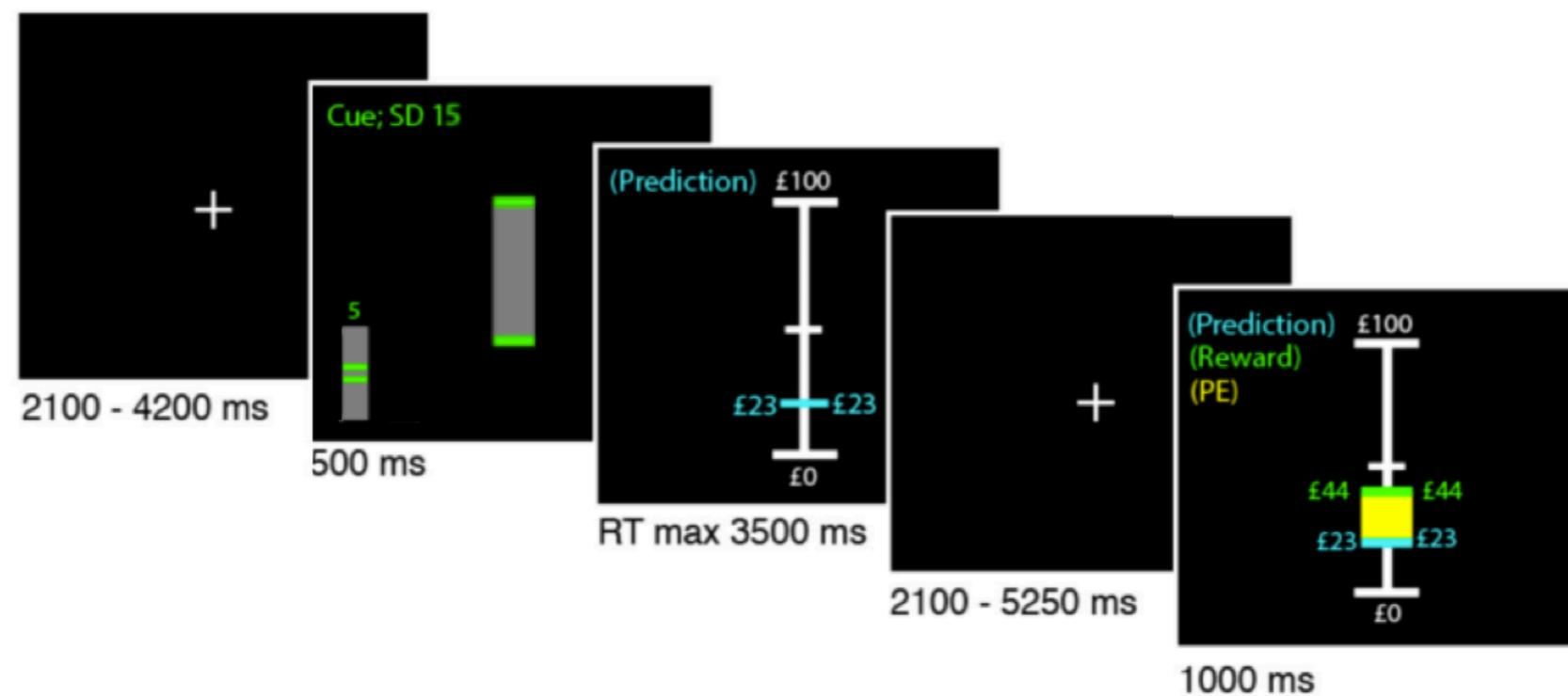
£0



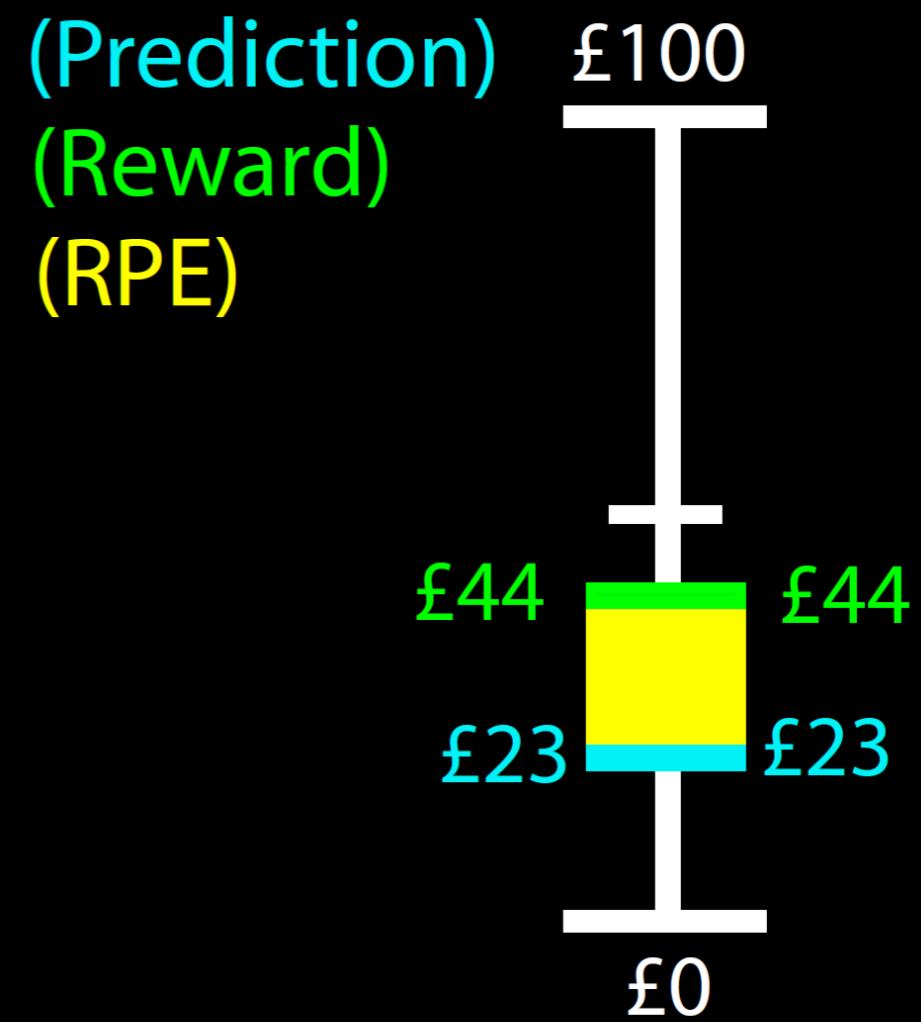
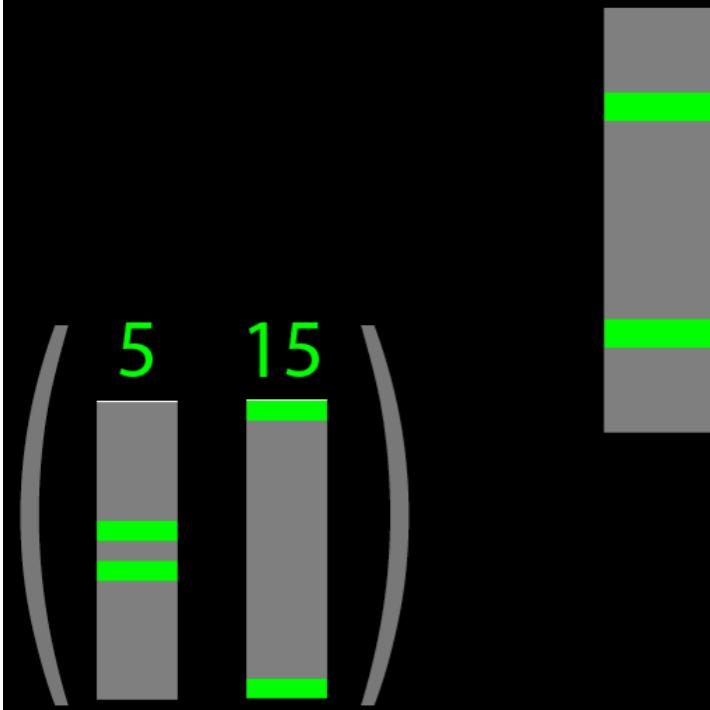


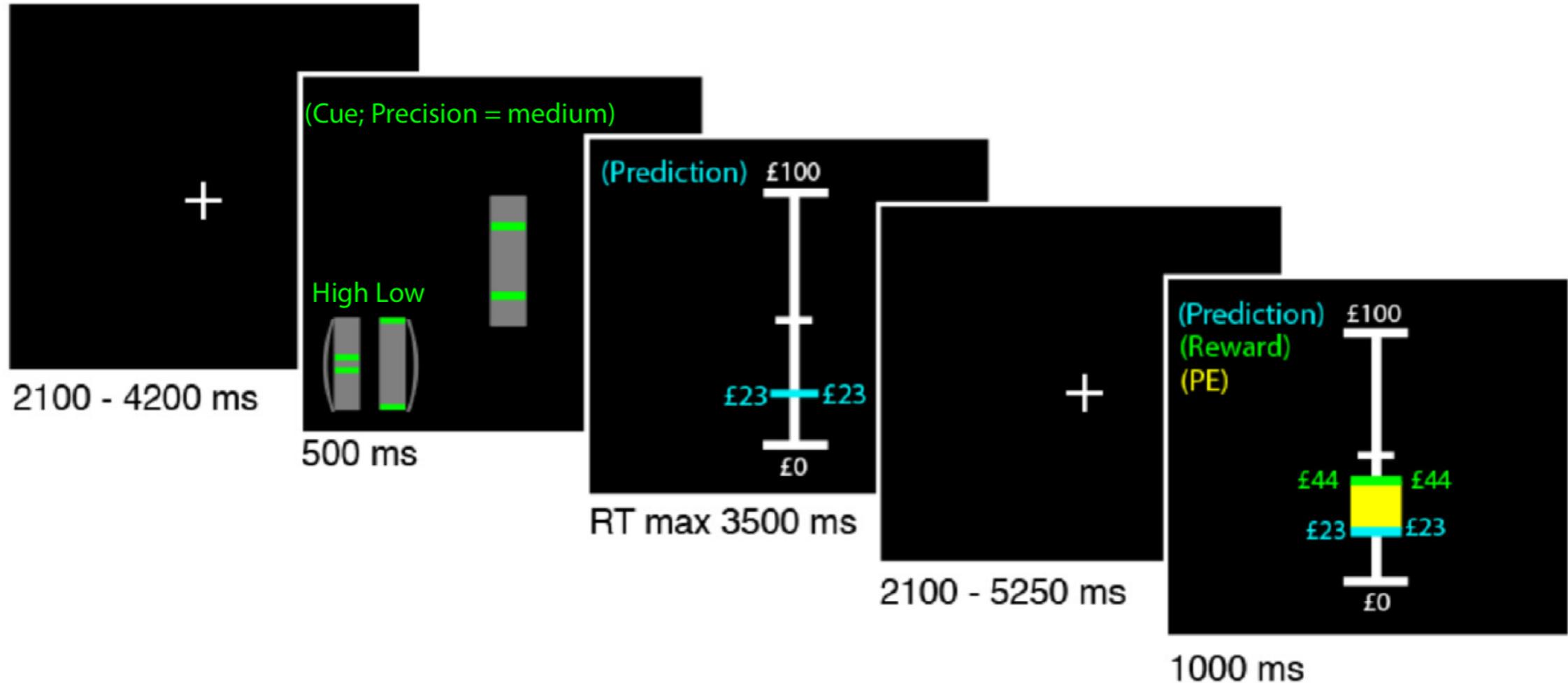
# Task structure

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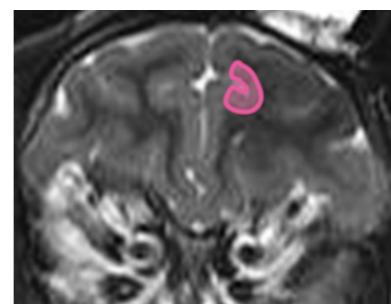


(Cue; SD 10)

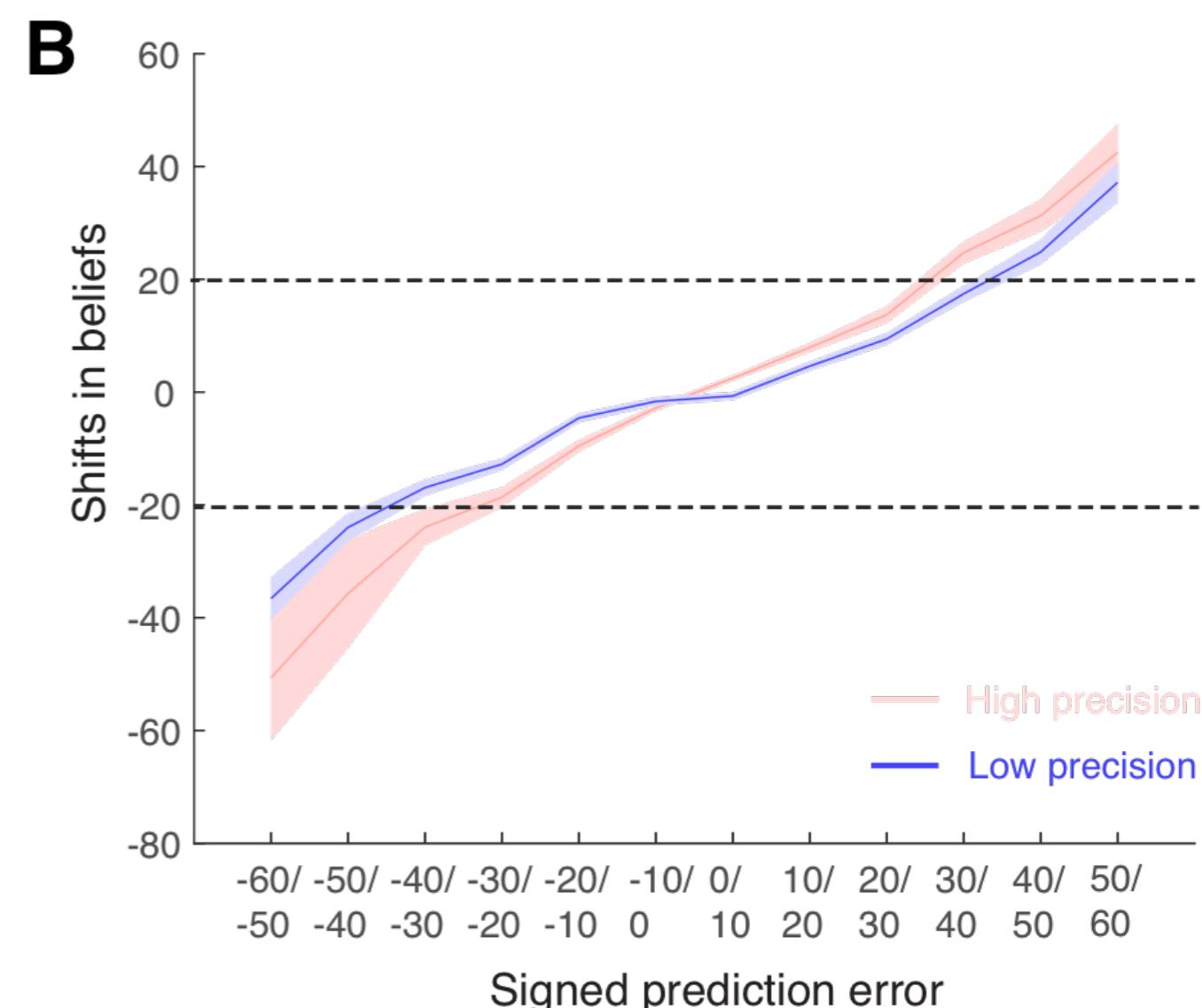
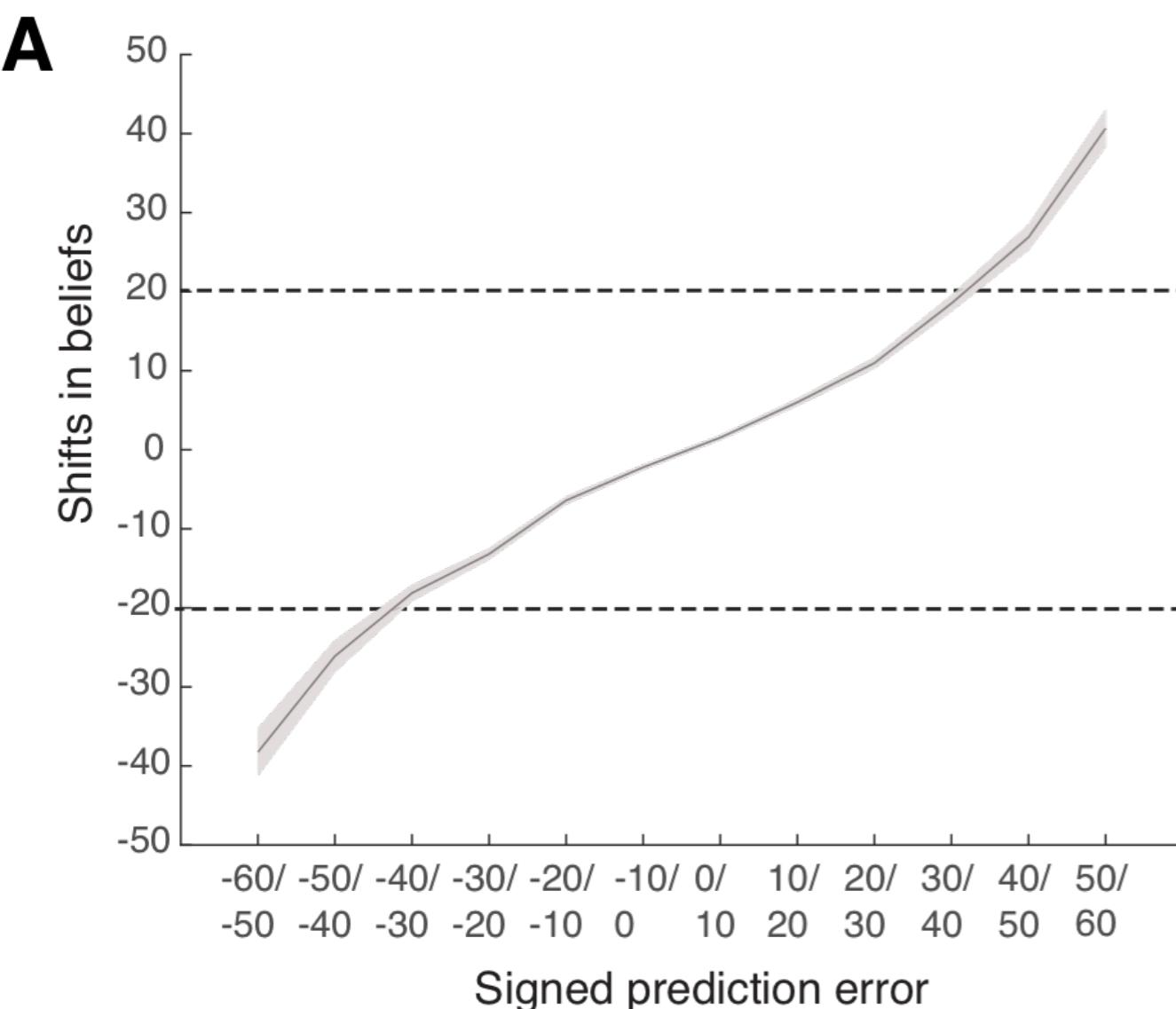




- Rewards drawn from a pot, with average value, and a spread. Spread can be wide or narrow. Your job - predict the size of upcoming rewards. Watch the actual reward and update your guess next time.
- Studied this in a trial of 59 healthy volunteers randomised to placebo, sulpiride, or bromocriptine. 186 trials per participant (~30 mins).
- Focus on “unsigned” prediction error (postulated to be a cortical signal - eg in monkeys Hayden et al 2011)



## Shifts in beliefs as a function of signed prediction error

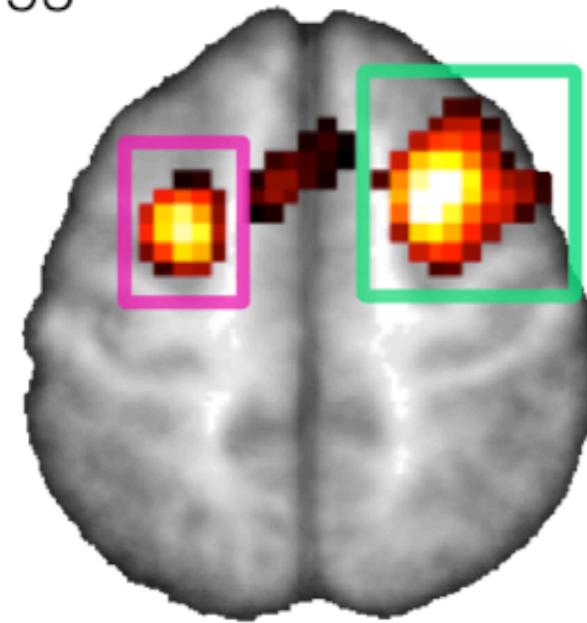


Signed prediction errors (x-axis) and belief-updating (y-axis) collapsed for precision (A) and separate (B)

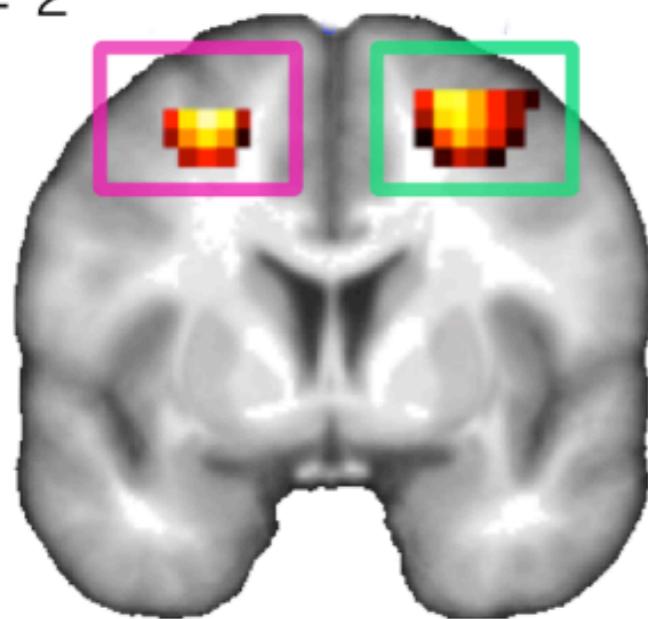
A: interaction effect between unsigned prediction error and signed prediction (above the top and below the bottom dotted line unsigned prediction errors are strongest, amplifying the effect of the signed prediction error).

B: the effect of precision: a stronger effect of signed prediction error in the high precision condition compared to low precision.

**A** Z = 53



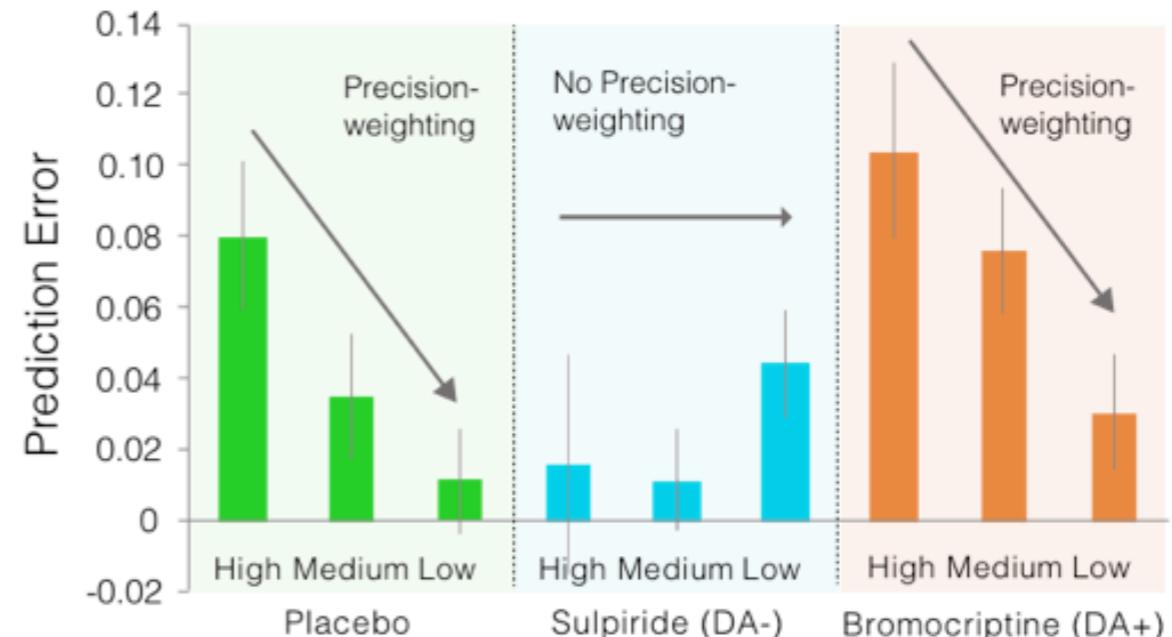
Y = 2



Unsigned PE signal  
Superior Frontal Cortex  
 $p < 0.01$  (corrected)

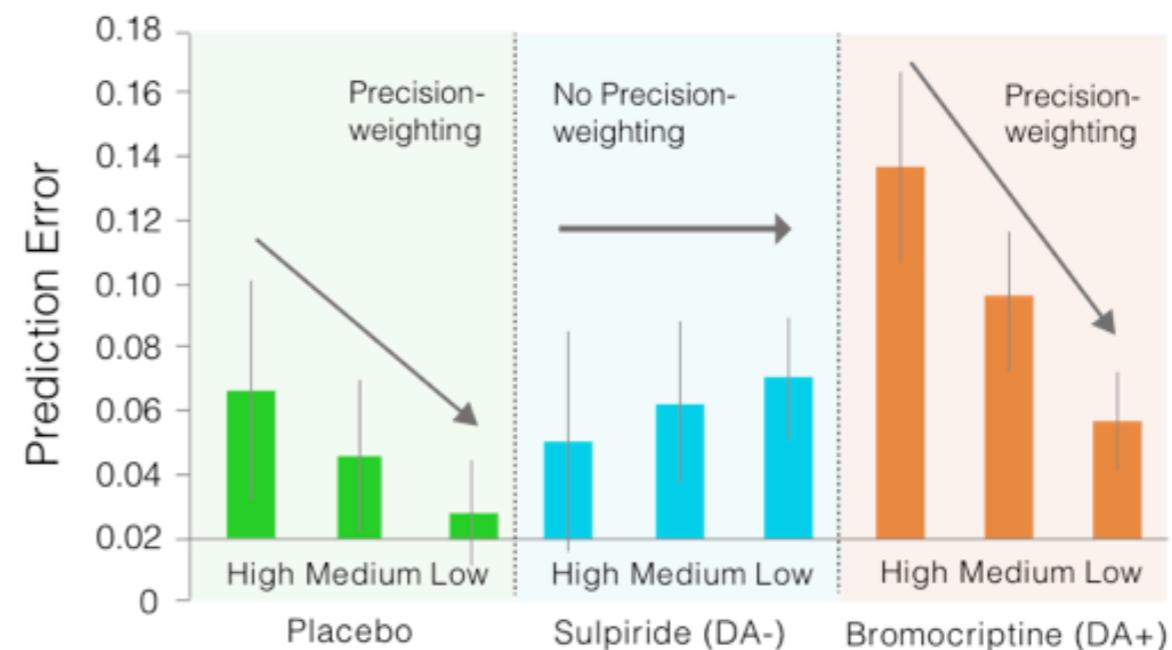
**B**

**Precision-weighting of unsigned prediction error in left SFC**



**C**

**Precision-weighting of unsigned prediction error in right SFC**



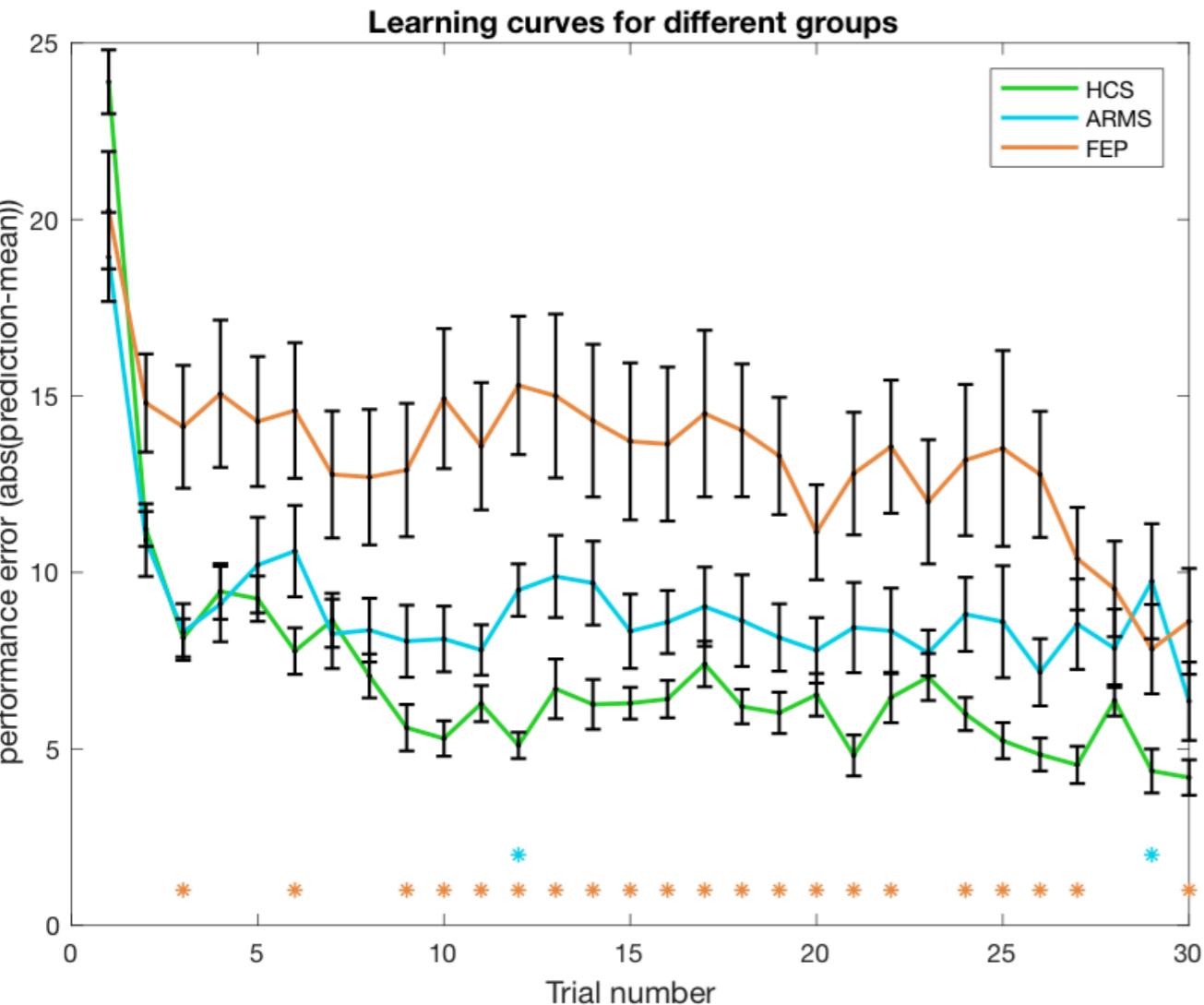
Interaction Drug \* Precision in Left SFC  $p=0.025$   
Haarmsa et al 2020 Molecular Psychiatry

# Summary

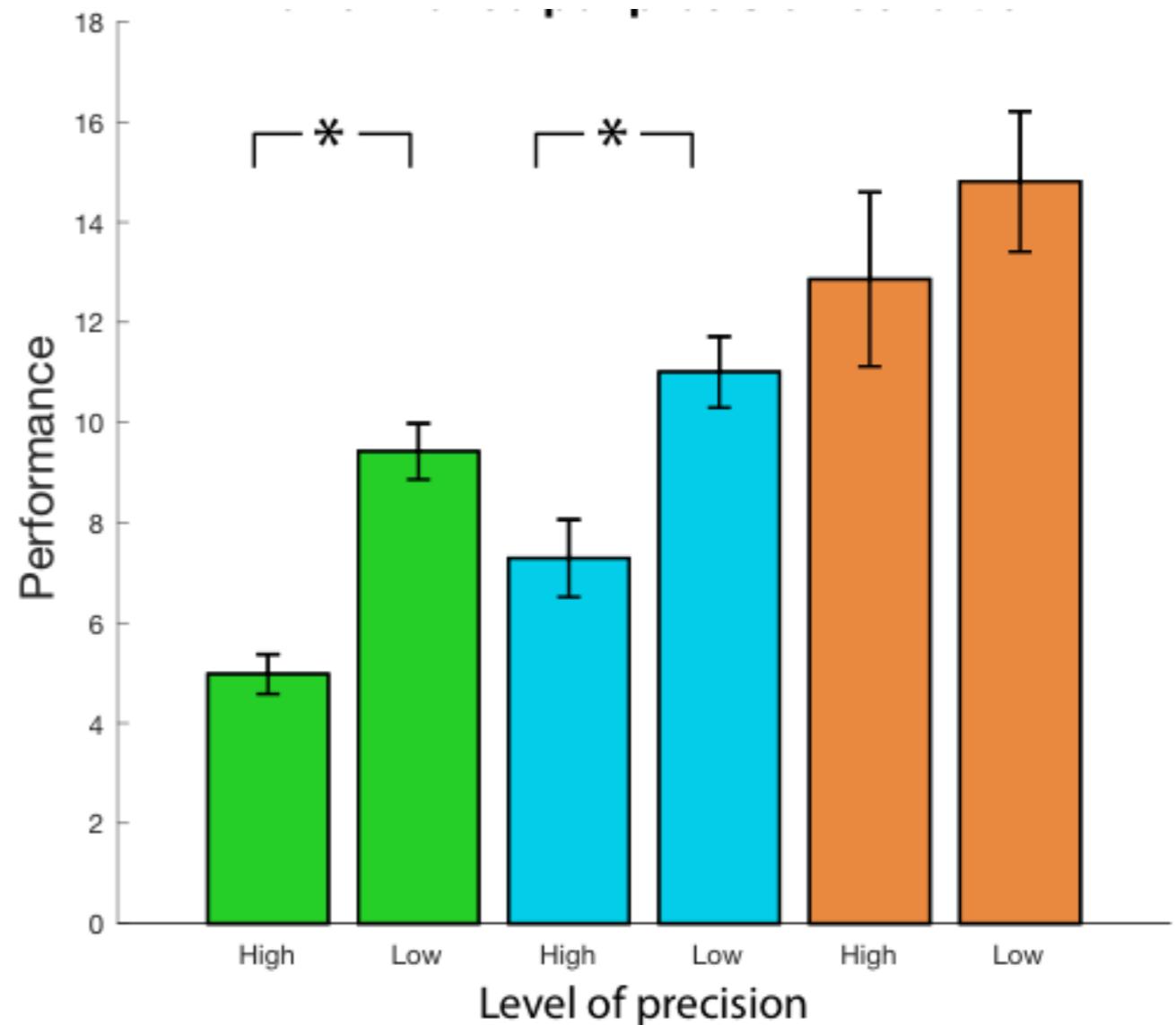
- Unsigned prediction error important for learning
- Encoded in human brain in superior frontal cortex
- This brain signal is precision weighted - stronger when environmental information is more precise, weaker when environment has greater variance
- The degree of precision weighting is modulated by dopaminergic medication
- What about in psychosis?

# Demographics

Group	HCS	ARMS	FEP			
N	30	24	26			
	Mean	SD	Mean	SD	Mean	SD
Age	22.57	3.53	21.00	3.48	24.7	4.90
Male	16		18		21	
IQ	118.8	10.5	118.7	11.65	105.8	19.8
PANSS positive	7.20	0.76	14.00	2.97	19.27	6.45
PANSS negative	7.23	.94	13.50	6.22	15.46	8.05
Taking antipsychotic medication	0/30		4/24		14/26	



- Better to have fast learning rate at first then slow later (seen in controls and ARMS).
- Learning rate steady in FEP



- Controls and ARMS perform better in high precision condition
- Modelling: Controls use precision weighting AND decaying learning rate. FEP: simple Rescorla Wagner learning.



# Computational modelling

## Rescorla-Wagner models

- Not precision-weighted (1 free parameter:  $\alpha$ )
- Estimated precision-weighting (2 free parameters:  $\alpha, \omega$ )

## Pearce-Hall models

- Not precision-weighted (2 free parameters:  $\alpha_1, \gamma$ )
- Estimated precision-weighted (3 free parameters:  $\alpha_1, \gamma, \omega$ )

## Rescorla-Wagner model

$$y_n = y_{n-1} + \alpha (\delta(\text{signed})_n / \omega)$$

$$\omega = 1 - \omega + \omega^*(\text{SD})$$

## Pearce-Hall model:

$$y_n = y_{n-1} + \alpha_n (\delta(\text{signed})_n / \omega)$$

$$\alpha_n = \gamma (\delta(\text{unsigned})_{n-1} / \omega) + (1 - \gamma) \alpha_{n-1}$$

$$\omega = 1 - \omega + \omega^*(\text{SD})$$

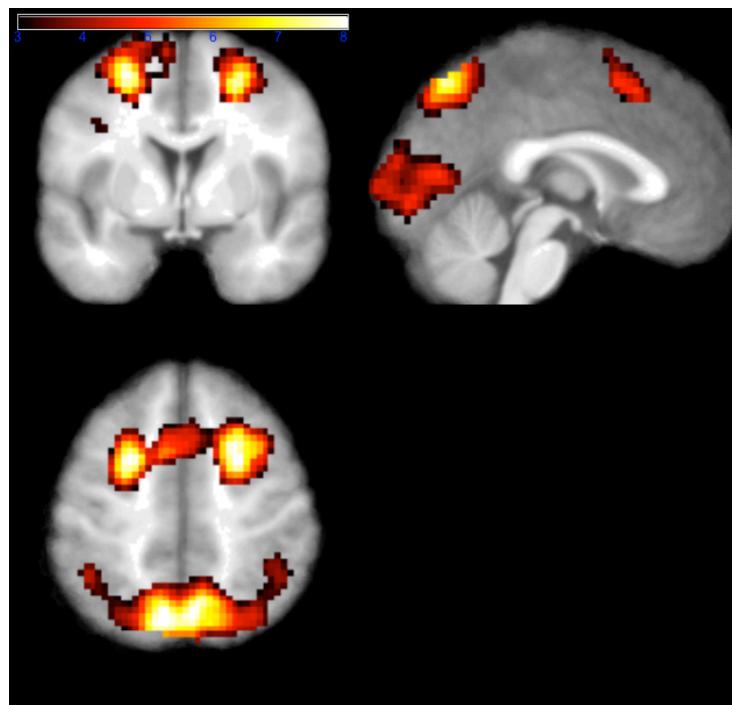
	Free parameters	AIC			
		Combined	HCS	ARMS	FEP
RW	1	1365.5	1361.1	1375.5	<b>1404.8</b>
RW <u>scaled</u>	1	1364.8	1311.7	1376.5	1406.3
PH <u>not scaled</u>	2	1359.8	1298.7	1362.0	1418.6
PH <u>scaled</u>	2	1361.4	1299.7	1362.9	1421.6
PH-estimated <u>precision</u>	3	1355.6	1292.9	1356.7	1428.6
PH-estimated precision separate for signed and unsigned PE	4	<b>1349.8</b>	<b>1288.6</b>	<b>1348.5</b>	1412.3

RW: Rescorla-Wagner. PH – Pearce-Hall.

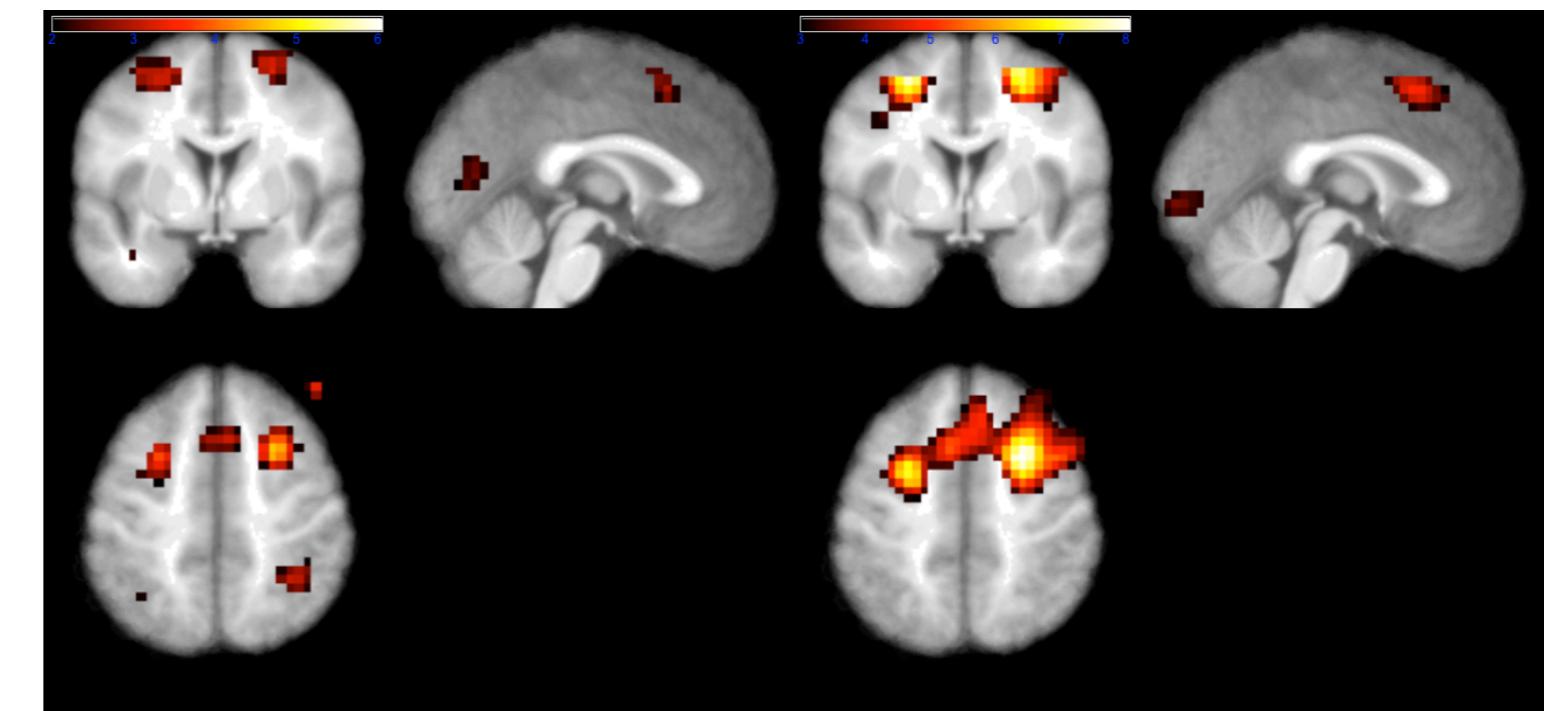
- Controls use precision weighting AND decaying learning rate.
- FEP: simple Rescorla Wagner learning.



# Unsigned prediction errors are encoded in superior frontal cortex

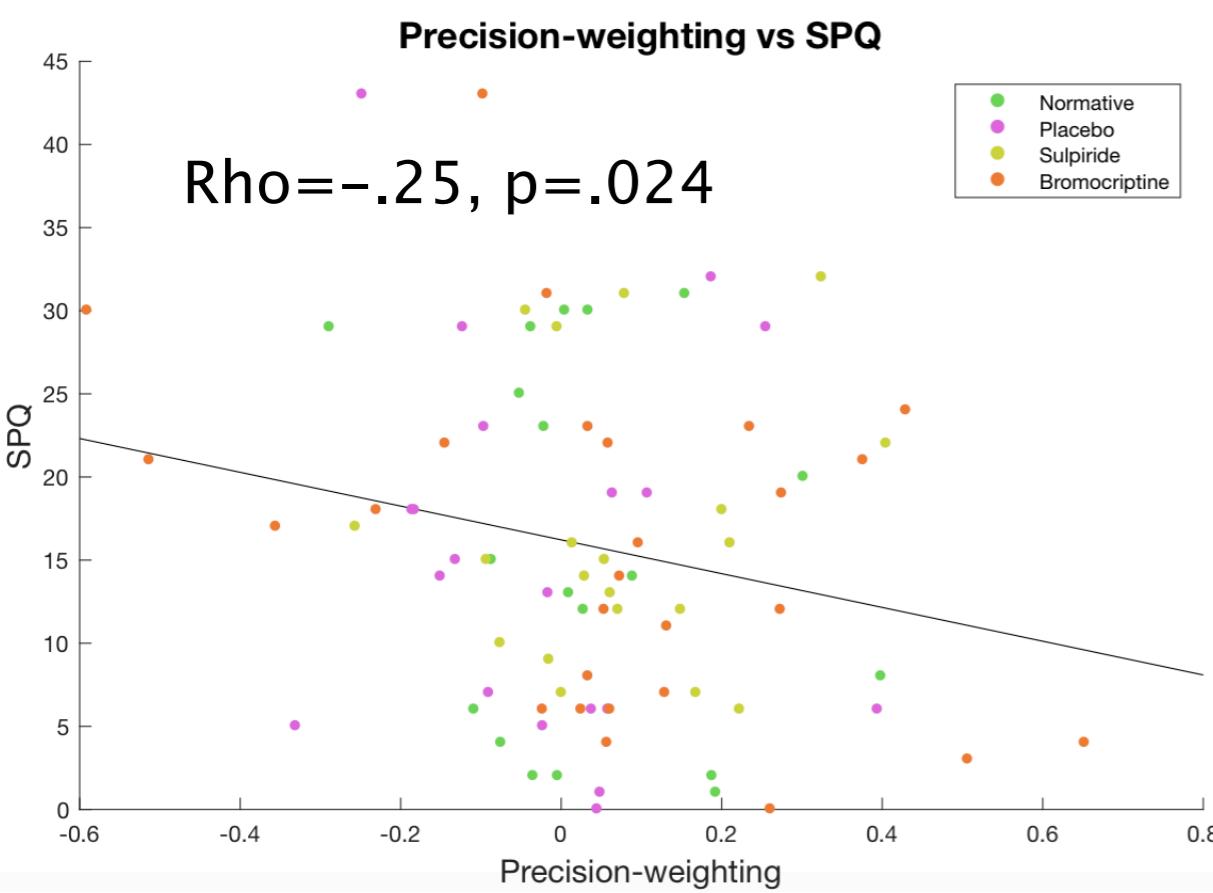
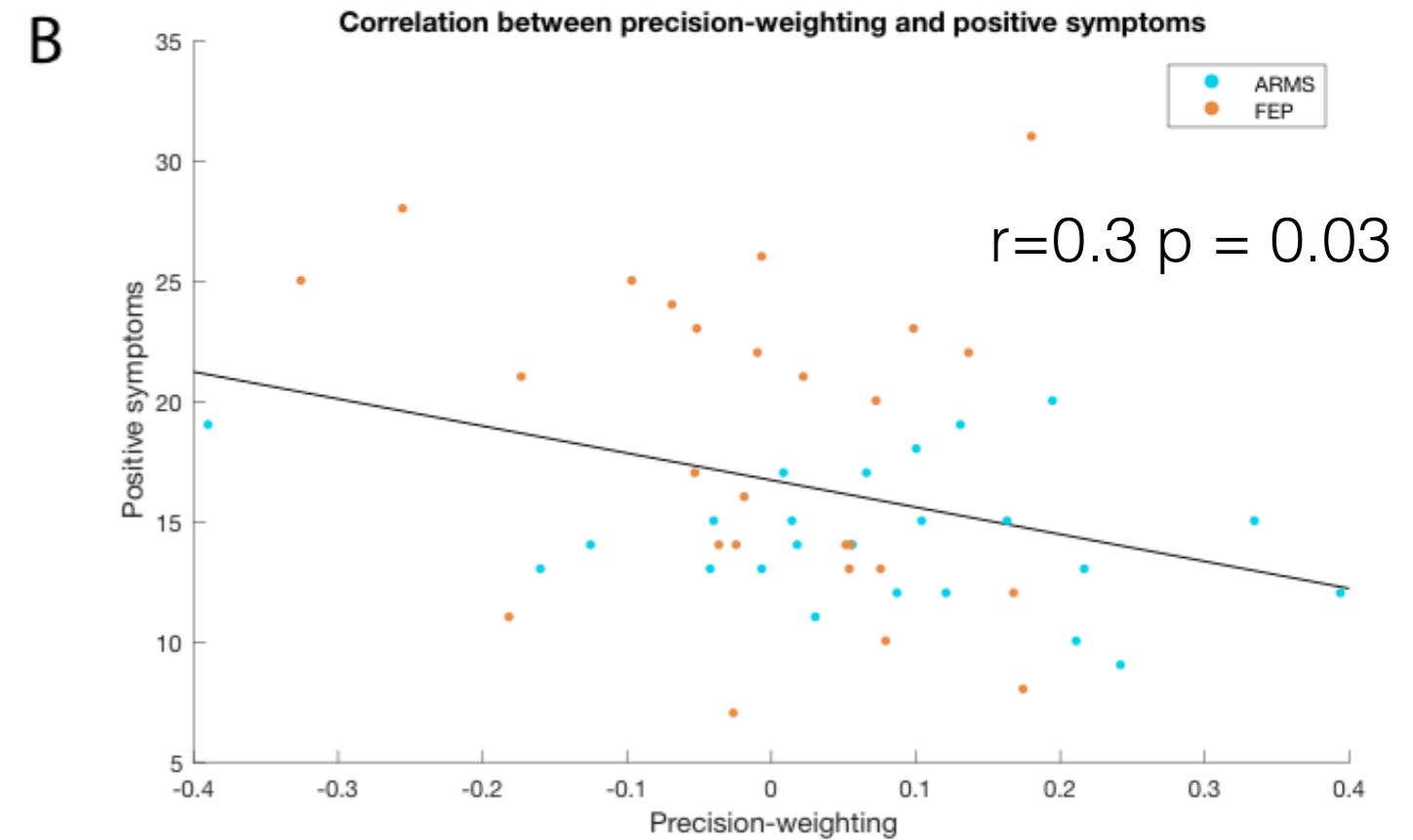
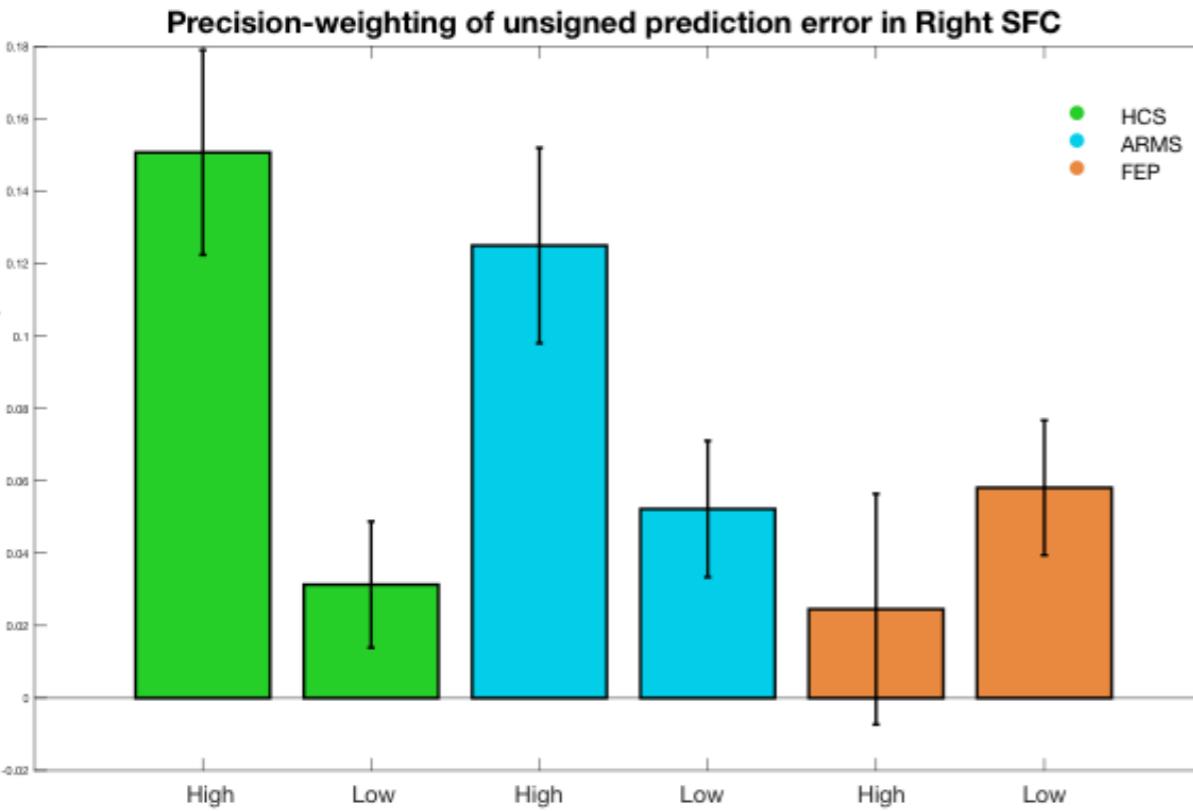


Psychosis study  
N=80



Healthy sample  
N=28

Dopamine drug study  
N=59



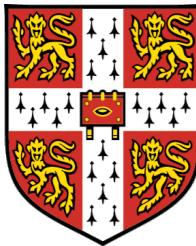
- Impaired precision weighting in Right SFC in psychosis ( $p=0.03$  SVC corrected)
- Degree of SFC precision-weighting is linked to symptom severity (pooling patient samples), though not when controlling for group ( $p=0.07$ )
- In 81 controls, SFC precision-weighting relates to schizotypy ( $p=0.024$ )
- SFC Precision-weighting predicts performance ( $p=0.001$ )

# Psychosis - precision and value of information

- Evidence of abnormalities in the way that decisions are made and associations and beliefs are formed in psychosis.
- Evidence of cortical dysfunction in representing environmental precision
- Potential role of dopamine (but may involve other neurotransmitters, monoamines etc.)

# Discussion

- Examples of how computational modelling can inform studies examining the pathogenesis of cognitive deficits and psychotic symptoms on schizophrenia spectrum disorders, possibilities of testing existing or novel drug effects
- Future work
  - Longitudinal studies in patients, link to health records, ‘omics
  - Much larger samples for patient and pharmacological studies
  - Opportunities for reverse translation (animal models being informed by human data)
  - Integrate pathophysiology & aetiology more closely



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